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# QUARTERLY

THE CHICAGO MEDICAL SCHOOL

VOLUME 7, NUMBER 3

JUNE, 1946

# Let your HEAD take you

*(The average American today has a choice of just going where "his feet take him", or choosing wisely the course to follow. Let's skip ahead 10 years, and take a look at John Jones—and listen to him . . .)*

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"Well, even after she got better, I stayed away from the weekly poker game—quit dropping a little cash at the hot spots now and then—gave up some of the things a man feels he has a right to. We didn't have as much fun for a while but we paid our taxes and the doctor and—we didn't touch the Bonds.

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# QUARTERLY

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# *Editorials . . .*

## OUR MEDICAL RESPONSIBILITY

The obligations of a medical institution can not be restricted to the teaching of past and present data regarding the etiology and treatment of most pathological entities. The mentor and his students have all delved into the study of medicine because of a keen curiosity in the makeup and function of the magnificent mechanics of "Life" and when studying, we learn of the many unsolved problems which still confound the old masters of the profession.

The metabolic processes are little thought of by the laymen, for they have no insight into the esoteric world of living, moving, electrically activated protoplasm which respires, digests, and lives on so that we as individuals may exist. The true doctor, however is also a true scientist and is curious as to the solutions of the problems of the day. The medical school must therefore have the facilities for investigation so that this natural scientific craving can be satisfied. We are proud of the work which has been going on in our laboratories at C.M.S.

Varied phases of pathological metabolic disorders; cancer and its seemingly unsurmountable barriers; tuberculosis, the partially tamed but still deadly enemy of man — are all being tackled boldly by our capable investigators, and we know that vitally essential positive or negative results will be published so that more light as to the true cause of these entities might be made known. One often wonders what goes on in the laboratories where sad faces reflecting failure change to eager elation over a period of a short time—or vice versa. That is the way of Science—you utilize your physical energies plus the cunning of the human brain in order to make Mother Nature reveal one more of her many secrets, and at times she will not divulge a thing. However we continue our work, modify our methods and hope that the future holds a reward for our tireless efforts.

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## A NEW ERA

We find the heart of the *Quarterly* devoted to the latest graduating class, another group of sixty men who have joined the ever increasing alumni of the Chicago Medical School.

Classes in the past have been awarded their doctorates at a time when the world was at war and the responsibilities of the Army doctor and civilian physician were emphasized to a greater degree. Emergency battle front surgery, vital trigger diagnoses, and tropical resistant disease entities were all major difficulties encountered on the battle fields—and night and day obligations to the lay-people by the one lone physician who cared for two to three thousand individuals, were problems that physicians of our and every other medical school had to cope with.

Today the emphasis on the responsibility of the physician is not as obvious, but in truth, the problems being faced by the general practitioner are as great as they have ever been. The ever present endemic diseases have had foreign and infrequent rare conditions superimposed upon them so that the task of differential diagnosis has been made all the more difficult. This is a new era in the practice of general medicine. The varied and sundry conditions enumerated in French's book on "Differential Diagnosis" must now all be taken into consideration, for the advantage of knowing geographical incident and distribution is no longer the great asset it has been in the past. Our soldiers have returned from Asia, Europe, South America, and the islands of the South Pacific bringing with them a textbook of parasitic, rickettsial, virus, and bacterial infections. Older physicians will therefore have to take out their books and relearn unused knowledge relating to these previously unseen diseases, and our medical students who intuitively have emphasized certain conditions will have to use their intuition a little more diffusely.

*Editor's Note: We would appreciate it if our readers would refer to our advertisers for the finest of products.*

# ALLOXAN DIABETES

Piero P. Foa, M.D., Ph. D
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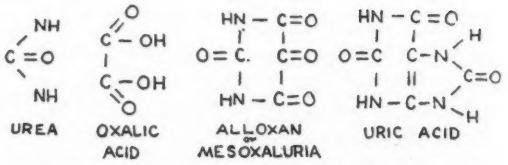
ONE day, toward the end of the eighteenth century in Strasbourg, the clinician Naunyn was walking through the court of the hospital where some dogs belonging to the department of Physiology were kept. Naunyn noticed that swarms of flies and other insects were feeding on the excreta of one group of dogs, completely deserting the excreta of another group. Analyzing a specimen of urine from a dog of the first group, Naunyn found that it was loaded with sugar. The dogs had been depancreatized by Mering and Minkowski and, at last, the cause of diabetes had been determined. The classical experiments of Mering and Minkowski (39) established that all the symptoms of diabetes could be produced in the dog by removal of the pancreas; this was the first type of experimental diabetes ever produced, and it led to the discovery and finally to the isolation and purification of insulin (5).

A decade after the discovery of insulin, Houssay and Biasotti (24) discovered that the removal of the pituitary gland in the diabetic dog results in the mitigation of the diabetes and, often, in the disappearance of hyperglycemia and glycosuria. The discovery of Houssay and Biasotti led to the investigation of the influence of the pituitary gland on the pancreas and the metabolism of carbohydrates and it was soon found that this gland secretes a hormone which is antagonistic to insulin and which, when injected into an animal, produces a second type of experimental diabetes called pituitary diabetes. As the investigation of the digestive functions of the pancreas and the keen sense of observation of a clinician led to the accidental discovery of pancreatic diabetes, so experiments on the crush syndrome led the English pathologist Shaw Dunn and his collaborators (14,15,16) to the accidental discovery of a third type of experimental diabetes, alloxan diabetes.

Alloxan had been known for many years; it is the ureide of oxalic acid and a close relative of uric acid, as can be seen from the following structural formulae:




Alloxan is a white powder, easily soluble in water and alcohol and must be used in freshly prepared solution as it hydrolyzes easily forming urea and mesoxalic acid. That alloxan has a pharmacological action was demonstrated first by Jacobs (27) who, in 1937, found that the intravenous injection of 70 to 100 mg of alloxan in the rabbit is followed by a severe progressive hypoglycemia, by convulsions which can be relieved with glucose and by death. As others demonstrated later, Jacobs had discovered only one phase of alloxan action and did not discover the hyperglycemic phase because his animals died too soon. Jacobs gave no explanation for his findings. Six years after the work of Jacobs, Dunn, Sheehan, and McLetchie (16) proved that, if the proper dose of alloxan is given and the animals live, a permanent diabetes can be produced. Dunn and his collaborators were interested in the biological action of substances capable of injuring the lower segment of the renal tubules and were investigating the histological changes produced by uric acid and related substances. Among these was alloxan, which they found capable of producing severe necrosis of the renal tubules and the islets of Langerhans.

The report of Dunn and his collaborators stimulated work by other investigators, and in a few months alloxan diabetes was produced in various animal species. It was found furthermore that alloxan can produce necrosis of the islet cells without injury to other tissues, if administered in proper doses (1, 9, 15).

*THE DISEASE.* The typical response to a single dose of alloxan consists of three stages: an immediate hyperglycemia reaching a maximum in 2 to 3 hours, a hypoglycemic phase lasting for several hours, often accompanied by convulsions and, finally, if the animal does not die during the second phase, an increase in blood sugar with glycosuria evident by the end of the

first or second day. The response of the individual animal to a single dose varies considerably, however, so that the duration and severity of the three phases is not a predictable constant and the diabetic phase may vary from a mild transitory type to a progressive fatal condition. The response to alloxan also varies from species to species. Owls, pidgeons, ducks and chickens, for instance, seem to be resistant to its action and these animals do not show pancreatic necrosis and do not develop diabetes (40, 46). According to the literature, the response of the rat is not constant and the experiments fail in about 40% of the cases, either because the animals do not become diabetic or because they die too soon. Rats, however, almost invariably become susceptible to alloxan if all food is removed for a period of from 48 to 60 hours preceding the injection (30).

The minimal dose of alloxan which will produce diabetes in 80% of the animals administered by a single intravenous or intraperitoneal injection varies from species to species. The following table (Goldner, modified, 18) gives the doses for the animals more commonly used; it is administered in 5% unneutralized solutions freshly prepared:

| | | | |
|---|---|---|---|
| Rat ..... | 200-300 | mg/Kg | i.p. |
| Rabbit ..... | 100-200 | mg/Kg | i.v. |
| Cat ..... | 150 | mg/Kg | i.v. |
| Monkey ..... | 100-150 | mg/Kg | i.v. |
| Pidgeon ..... | 125-200 | mg/Kg | i.v. |
| Dog ..... | 50-100 | mg/Kg | i.v. |
| Bufo arenarum | 200 | mg/Kg | i.v. (25) |
| Rana pipiens | 150-220 | mg/Kg | i.v. (47) |

(contrary to the findings of others, 46)

The margin between the fatal and the diabetogenic dose is widest in the rabbit, rat and dog, which makes these animals the animals of choice. Diabetes mellitus develops about 24 hours after the injection of alloxan; hyperglycemia, glycosuria, polyuria, polydipsia, polyphagia and loss of weight are present and the clinical picture is very similar to that of human or pancreatic diabetes. Unless insulin is given the animals lose weight rapidly, develop hyperlipemia and fatty degeneration of the liver, become very susceptible to infections and die in six to eight weeks in complete emaciation. Ketosis does not always develop. Dogs are particularly resistant to this metabolic disturbance although they develop acidosis easily after pancreatectomy. On the other hand, monkeys, which do not always develop severe diabetes after removal of the pancreas, have marked hyperglycemia and glycosuria and develop acidosis very early after the injection of alloxan. Rats show a very severe picture and, if not treated, usually die within ten days with Ketonuria and an output of urine which may exceed 10% of the body weight. Rabbits may develop severe diabetes with acidosis and die of emaciation or intercurrent infection as do dogs, monkeys and rats, but in other instances they show a remarkable resistance and are capable of compensating for the loss of glucose by increasing their food intake, thus appearing in excellent health. All symptoms of diabetes may disappear in the rabbit, only a decreased tolerance for carbohydrate remaining as a sign of pancreatic deficiency.

As stated above, typical diabetes does not develop until after a short hyperglycemic and a longer hypoglycemic phase; during the latter, the animals must be kept under constant observation as many develop fatal hypoglycemic convulsions. Alloxan diabetic dogs can be kept alive for an indefinite period of time with approximateiy 1 unit of insulin per kilo of body weight, although individual adjustments are often necessary (18). According to Ruben and Yardumian, alloxan will produce diabetes in rats also if administered orally (45). When alloxan is injected into a pregnant animal, the blood sugar of the fetus parallels that of the mother, although at a different level. After birth the offspring show no signs of diabetes and their pancreases are normal (17).

Associated with the severe glycosuria there is a loss of glycogen from the liver and the skeletal muscle, but not from the heart, and this fact reveals a fundamental metabolic difference between the two types of muscle (32). Hyperlipemia is frequently marked (1) and is associated with hypercholesterolemia (31) and fatty infiltration of the liver (18). Studies with deuterium revealed that the synthesis of fatty acids from glucose is decreased to about 5% of normal in the alloxan diabetic animal; it is probable, therefore, that the excess fat found in the plasma and in the liver is derived from the fat depots (49). Other metabolic disturbances consist in a rise of the inorganic phosphate which, in coma, can reach the value of 26 mg % and is associated

with a decrease in the organic phosphorus compounds of the liver (29) and, in pidgeons, a rise in the blood uric acid level to 100 times the normal value, associated with large deposits of sodium urate crystals on the serous membranes and in the kidneys. This condition has been known for a long time as "visceral gout" (18).

The clinical syndrome of alloxan diabetes is associated with a pathological picture which is characteristic. The pancreatic changes, described first by Dunn, Sheehan and McLetchie in the rabbit (16) consist of acute necrosis of almost all the islet cells, starting at the center of the islet in proximity to the blood supply (14). Although the alpha cells of the islets of Langerhans may suffer from alloxan, the most characteristic lesion is the disappearance of the beta cells, following granulation and shrinkage of the entire cell body (19). There is no hydropic degeneration which is so prominent in pituitary diabetes, although it can be induced by repeated small doses of alloxan (2). The lesions of the beta cells are apparent five minutes after an intravenous injection of alloxan (2, 26) without any sign of inflammatory reaction. In dogs the pancreatic ducts usually show a characteristic vacuolization (18).

An interesting study of the pathologic lesions following the intravenous administration of 200 mg/Kg of alloxan in the rabbit was made by Bailey, Bailey and Hagan (2). These authors studied the progression of the pancreatic lesions as well as of the lesions in other organs through the three stages of alloxan diabetes, namely the transitory hyperglycemia, the transitory hypoglycemia and the permanent hyperglycemia. During the first stage degenerative changes begin in the islet cells very quickly after the injection of alloxan (a few minutes as stated above) and progress steadily through the second stage toward the fully established permanent lesions associated with diabetes in the final phase. In the latter the total number of islets is very small, suggesting that some have disappeared completely, and those which remain are composed entirely of alpha cells. When diabetes is produced by the injection of small repeated doses of alloxan, several mitoses are observed indicating that some of the islet lesions are reversible. The acinar tissue remains normal throughout the development of the disease.

By the use of proper doses of alloxan, the pathologic lesions can be limited to the beta cells of the insular tissue, except for a mild and temporary degeneration of the tubular opithelium of the kidney, mild fatty metamorphosis of the liver and some congestion of the adrenal glands. If amounts of alloxan greater than the diabetogenic dose are given, necrosis of the renal convoluted tubules, severe rise in NPN and albuminuria can be observed, as well as fatty degeneration and necrosis of the liver, congestion, necrosis and leucocytic infiltration of the adrenal cortex and hydropic degeneration and necrosis of the anterior pituitary (15, 16, 19, 23, 31, 45). Of special interest is the development of cataracts which, as described by Bailey, Bailey and Leech (3), corresponded in all respects to the development of cataracts in human diabetic patients both histologically and as viewed by slit-lamp. Cataracts seem to develop more quickly and progress to complete opacity faster in rabbits will poorly controlled diabetes than in those receiving insulin.

PATHOGENESIS. In the discussion of the pathogenesis of alloxan diabetes the three phases of its action may well be considered separately. First in order of time is, as we have seen, the initial hyperglycemic phase. This conceivably could be due either to an inhibition of insulin action or to a mobilization of extra glucose. The first possibility was ruled out when it was shown that alloxan does not inactivate insulin in vitro and that if insulin is injected simultaneously with alloxan the initial hyperglycemia will not develop (19). It seems likely therefore that this phase of alloxan action is due to a mobilization of extra glucose. Such glycogenolysis may occur in the liver under the influence of epinephrine, in which case the initial hyperglycemia should not occur if the adrenals are removed. This was demonstrated by Goldner and Gomori (19) and it is supported by the observation of Hard and Carr (23) who showed evidence of histological changes in the adrenal medulla immediately following an injection of alloxan. Other authors do not agree that the hepatic glycogenolysis is due to epinephrine. Peralta (41), for instance, found that the initial alloxan hyperglycemia appears even when the adrenals are removed, but not when the hepatic nerves are cut and the adrenals left intact, and Houssay, Orias and Sara (25) found that it appears after adrenalectomy

and after section of the splanchnic nerves, but not after hepatectomy or evisceration. Houssay and collaborators conclude that the hyperglycemia is due to a direct action of alloxan on the liver.

The second phase of alloxan action, that of a temporary severe hypoglycemia, was at first interpreted as due to an insulin-like effect of alloxan itself. This hypothesis was discarded, however, when it was shown that alloxan does not have a hypoglycemic effect in animals previously treated with alloxan, depancreatized (19, 44) or eviscerated (12). The presence of a normal pancreas seems necessary, therefore, for the occurence of the hypoglycemic phase. If the hypoglycemia is due to the effect of alloxan upon the pancreas, two mechanisms for its production are possible. They are that alloxan may stimulate an overproduction of insulin or that preformed insulin may be suddenly released by the destruction of the islet cells. The first hypothesis was suggested by Dunn and his co-workers (14, 15, 16) and is supported by the statement of Lichtwitz (34) that "'A hypoglycemic phase following a hyperglycemic reaction indicates an abnormally strong stimulation of the islet system." That the hypoglycemic phase is due to the liberation of insulin from the necrotized islet cells was suggested by several investigators (2, 19, 26). In the first place, it was shown that the initial hyperglycemia, which, according to the theory of insulin over-production is its physiological stimulus, can be prevented by the injection of insulin with alloxan without modifying the subsequent hypoglycemic reaction. Secondly, beta cell degeneration precedes the hypoglycemia (2) and whenever the animal survives it is impossible to separate the hypoglycemic effect from the diabetogenic action of alloxan, which always develops.

A recent paper by Banerjee (4) also brings evidence against the theory of over-stimulation of the islet cells. The author removed part of the pancreas of rabbits leaving just enough tissue to maintain a normal fasting blood sugar. If alloxan stimulates the islet cells to the extent of producing subsequent necrosis due to overwork, the remaining pancreatic tissue should secrete enough insulin to produce marked hypoglycemia in the partially depancreatized rabbits. This did not occur and the slight hypoglycemia observed could be better explained by the liberation of small amounts of insulin from the relatively few necrosed islet cells still present in the animals.

A third possible explanation for the hypoglycemic action was suggested by Houssay, Orias and Sara (25). According to these authors, this phase does occur in the depancreatized animal and, therefore, must be extrapancreatic in origin, and probably due to a decrease in hepatic glucogenesis. The findings of Houssay and his collaborators have not been confirmed as yet.

It appears that the initial hyperglycemic reaction is due to over-activity of the adrenal medulla and the hypoglycemic phase which follows to a sudden liberation of preformed insulin. The whole blood sugar curve can be simulated by the injection of two subcutaneous doses of epinephrine followed by the injection of 10 units of Protamin Zinc Insulin (26). The third phase of alloxan action, that of permanent hyperglycemia, is due to the permanent necrosis of the islet cells and therefore to the permanent lack of insulin production. Investigators, however, do not agree on how this necrosis comes about. One group (14, 15, 16, 37) believes that alloxan stimulates the adrenals and thus produces the initial hyperglycemia. This in turn constitutes a stimulus to the over-production of insulin resulting in the second, or hypoglycemic phase, and terminating in death of the islet cells due to overwork. The weight of experimental evidence, however, favors the hypothesis of Goldner and Gomori (19), that alloxan has a direct necrotizing effect on the islet cells which would result first in the liberation of pre-existing insulin and then, when this is exhausted, in permanent diabetes. This view is supported by the following experimental evidence: 1) Clamping the blood supply of a portion of a dog's pancreas during and for 1 to 6 minutes after the injection of alloxan protects that portion from damage, while in the rest the beta cells degenerate; and, 2) The initial hyperglycemia can be prevented by insulin, phlorhizin or starvation, the following hypoglycemia by the injection of glucose, yet beta cells will degenerate and diabetes develop.

It seems likely, therefore, that alloxan has a specific necrotizing action on the insulin-producing cells of the pancreas resulting in the libera-

tion of preformed insulin and terminating in a true permanent pancreatic diabetes. A confirmation of this view is found in the fact that the alloxan-treated pancreas contains only about one-fourth the amount of insulin found in the normal organ (19, 44). It is possible that the action of alloxan may be enzymatic in nature as alloxan in low concentration may act as a hydrogen acceptor for certain dehydrogeneses. Some specific enzyme in the beta cells may have a high affinity for alloxan and be inactivated by union with it (6, 13). According to Goldner (18), alloxan can be easily reduced to dialuric acid with which it forms a redox system and its structure is found as a constituent part of the flavine molecule.

Alloxan diabetes resembles pituitary diabetes and surgical diabetes of partial or total pancreatectomy in its fundamental symptoms, but it differs from them in many significent respects, although all three are considered the result of beta cell degeneration (42, 43, 52). The main differences are as follows:

1) Diabetes due to partial pancreatectomy and pituitary diabetes are caused by degeneration of the beta cells due to overwork. Both can be prevented by starvation or by insulin in the early stages of the disease. Alloxan diabetes cannot be prevented by starvation or insulin and it is due to the direct action of alloxan on the beta cells.

2) Alloxan is effective in a single dose; pituitary extract must be injected over a period of several days.

3) Some species (rat) can be made diabetic with anterior pituitary extract only after extensive pancreatectomy alloxan is active in the intact animal.

4) Monkeys, who are very resistant to pancreatectomy, develop severe alloxan diabetes.

5) Anterior pituitary extract diabetes is more insulin resistant than alloxan diabetes, whereas an alloxan diabetic has much greater hyperglycemia and glycosuria and requires more insulin than a depancreatized one (50).

6) Despite its greater insulin requirement, the alloxan diabetic animal can live much longer than the depancreatized one without insulin and often fails to develop ketosis and diabetic coma (50).

7) The extremely high blood sugar suggests that alloxan may damage the liver cells also (19).

8) The histologic changes produced by anterior pituitary extract in the beta cells are mitosis, degranulation and vacuolization ending in atrophy and hyaline changes. Alloxan produces irreversible acute degeneration without vacuolization or fibrosis.

9) Adrenalectomy improves alloxan diabetes (28) and it produces effects similar to those described by Long and co-workers (36, 37) in depancreatized animals.

*THE MEANING OF ALLOXAN DIABETES FOR THE PHYSIOLOGY AND PATHOGENESIS OF DIABETES AND THE UTILIZATION OF ALLOXAN IN HUMAN THERAPY.* As was mentioned above, Thorogood and Zimmermann (50) found that, despite the much higher insulin requirement of the alloxan diabetic than of the depancreatized dog, the former can be deprived of insulin for a much longer period of time without developing acidosis and coma. Thorogood and Zimmermann made another interesting observation, namely that removal of the pancreas will decrease the insulin requirement of the alloxan dog to one-third, but the animal will quickly pass into coma when not controlled with insulin. They suggest that the alpha cells of the islets secrete a second pancreatic hormone which increases the blood sugar, but prevents ketosis. The alpha cells, as we have seen, are not injured by alloxan but are, of course, removed by pancreatectomy. It is possible that, according to the views of Soskin (48), the high blood sugar itself may prevent ketosis, by allowing a greater utilization of carbohydrate in the alloxan diabetic animal. This possibility could explain the fact, observed by Burn, Lewis and Kelsey (11), that when an alloxan diabetic animal is fed a high fat-low carbohydrate diet, glycosuria diminishes and ketonuria appears. The concept of two pancreatic hormones, one regulating blood sugar and one ketosis, is a very interesting one and could explain the different tendencies towards ketosis in different diabetic patients and also the small insulin requirements of completely depancreatized men.

An observation of interest for the dietary management of human diabetes was recently made

(*Continued on page* 28)

# RECENT DEVELOPMENTS IN CREATIN - CREATININE METABOLISM WITH POSSIBLE CLINICAL APPLICATION

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CREATINE, or methyl guanidine acetic acid, is the chief nitrogenous extractive of the muscles and serves as the principle storehouse for phosphate since about 70 per cent of the available phosphate is combined with creatine as creatine phosphate. Creatinine, the anhydride of creatine, is excreted into the urine. The following views were widely accepted until recently in regard to the metabolism of these two substances:

(1) Creatine and creatinine formation occurs in the tissues as the demand for them arises, i.e. they are not formed from the protein of the diet.

(2) This makes them both products of the endogenous nitrogen metabolism the extent of which is largely represented by the excretion of creatinine in the urine.

(3) Urea excretion, which varies directly with the protein intake, largely represents the extent of the exogenous nitrogen metabolism.

(4) The excretion of creatinine is influenced by the body weight of the individual and the creatinine coefficient is defined as the mgs. of creatinine (or creatinine N) excreted daily per kilo body weight.

(5) Creatine is dehydrated into creatinine and this reaction is irreversible in the body.

(6) The ingestion of 1.32 gm. of creatine (the creatine tolerance test) with subsequent determination of the retention and excretion of creatine, is supposed to be a type of tolerance test for creatine in the myopathy patient somewhat analogous to the glucose tolerance test in the diabetic. The more creatine retained by the patient the better his state of muscular tissue.

These views are still held by many biochemists and clinicians at the present time. In this article I will outline the recent developments in the field with their possible clinical applications.

The results of my first observation in this field obtained at Western Reserve Medical School in Cleveland showed that body weight had nothing to do with the creatinine output in 400 medical students who ingested a normal, high and low protein diet, ($r=0.13 \pm 0.03$ between creatinine and body weight on all three diets). From this result it was concluded that the creatinine coefficient had little, if any, physiological significance. (1) These results have been confirmed a number of times (2, 3) and shows that creatine and creatinine both must arise from the amino acids and proteins of the diet, the view generally held by the older biochemists before 1905. It was soon observed that practically all of the amino acids of the protein molecule when injected or ingested by rats and ingested by man would cause increases in creatine formation in the muscles and in creatinine excretion in the urine (2).

A review of the literature for the last 16 years has recently been published (3). Some of the newer points of view in the field are as follows:

(1) Creatine and creatinine are not products of an endogenous nitrogen metabolism as compared to an exogenous nitrogen metabolism. No distinction is to be drawn between these two types of metabolism. (1, 3) This view was later confirmed by the late Professor Schoenheimer using his tracer technique. (5)

(2) Creatinine excretion is not dependent upon the body weight and the creatinine coefficient has little physiological or clinical significance. (29)

(3) The reason for the supposed constancy in the creatinine output is due to the fact that the individual is usually in nitrogen and water balance. Increases in protein or water intake will increase creatine and creatinine excretion. (3)

(4) Administered creatine is not changed into creatinine in the rat and man (This statement is based upon the results of 10 studies using the Jaffe reaction with alkaline picrate). Schoenheimer, however, using 3 adult rats, showed that traces of $N^{15}$ from creatine were found in creatinine, thus showing the possibility of the trans-

formation in the tissues. (26) In any case the creatine-creatinine transformation in the tissues is reversible since administered creatinine takes up a molecule of water to form creatine in both the rat and man. (3)

(5) The tissues contain a *creatine* and *creatinine oxidase* which cause the oxidation or disappearance of creatine and creatinine, respectively. *Creatinine hydrase* causes the transformation of creatinine into creatine and no creatine hydrase, for the transformation of creatine into creatinine, occurs in the tissues of the rat. Water, or physiological saline, ingested or injected, in the rat or man, causes an increase in the excretion of creatine and creatinine.

(6) The creatine tolerance test is simply a creatine oxidation test and as such has little clinical significance.

(7) Creatinuria is not due to a breakdown of glycogen (Brentano) but to a lack of phosphate in the tissues to hold creatine in the muscles as creatine phosphate. (4) Glycolysis, with a liberation of phosphate, causes creatine retention rather than increases in creatine excretion.

(8) Creatine and creatinine are formed from any amino acid of the protein molecule, except proline and oxyproline. This shows the importance of the amino group of the amino acid in creatine formation. Schoenheimer, *et al,* (5) observed that ammonia containing $N^{15}$ was changed into creatine containing $N^{15}$. Other amino acids, such as methionine (or choline) can furnish the methyl group necessary for creatine and creatinine formation. (3) (8)

(9) This methylation process is necessary to prevent the formation of fatty livers (6) and hemorrhages in the kidneys (7), facts destined to be of much clinical importance in the future. (32)

(10) Administration of glycine (amino acetic acid, the simplest of all of the amino acids) serves to increase creatine formation in diseases of the muscles and heart (9, 13, 14) and to increase the energy output of a normal average individual (10, 11, 12). Improvement also occurs in some clinical conditions, such as myasthenia mitis and gravis, etc. (3, 13) and in the myopathies. (3, 13, 14)

No. 10 would seem to be of the most clinical importance but before discussing it further let us first consider the chemistry of muscular contraction. It was first shown by Hill (15) that the energy for the contraction was derived from glycolysis. Lundsgaard (16), however, showed later that a muscle poisoned with iodoacetic acid would contract for a time before the production of lactic acid and he suggested that it was the breakdown of creatine phosphate that supplied energy for the contraction. But it remained for Lohmann (17) to show that neither of these views tell the whole story. He showed that it was the breakdown of adenosinetriphosphate which supplied the energy for contraction. We have, therefore, learned the chemistry of muscular contraction backwards. The modern view is somewhat as follows:

1. Adenosinetriphosphate ⟨——⟩ Adenylic acid + 2 Phosphate (bond energy) (Adenosinetriphosphatase).
   (*Energy for Contraction*)
2. Creatine Phosphate ⟨——⟩ Creatine + Phosphate (bond energy).
   (*Energy for Resynthesis of Adenosinetriphosphate*)
3. Glycogen ——⟩ Lactic acid (phosphate bond energy).
   (*Energy for the Resynthesis of Creatine Phosphate*)
4. Oxidation of a small part of the lactic acid. (Energy for resynthesis of the remainder of the lactic acid to glycogen.)

Meyerhof (18) has listed the following reactions which occur in the anaerobic recovery of muscle:

A. ½ Hexosephosphate ——⟩ Lactic acid + Phosphate + 16,000 cal
   heat of neutralization in muscle + 8,000 cal
   + 24,000 cal.

B. Creatine Phosphate ⟨——⟩ Creatine + Phosphate + 11,000 cal.

C. Adenylic Acid + 2 Creatine Phosphate ⟨——⟩ Adenosinetriphosphate + 2 Creatine + 0 cal.

D. Adenosinetriphosphate —⟩ Adenylic acid + 2 Phosphate + 22,000 cal.

E. = C + D. 2 Creatine Phosphate ⟨——⟩ 2 Creatine + 2 Phosphate + 22,000 cal.

Rapid advances have recently been made in our knowledge of the chemistry of glycolysis and

glycogenesis. Many enzyme reactions occur here accompanied by phosphate carriers, coenzymes and inorganic catalysts. Most of these enzymes have been isolated in crystalline form. While no scheme at the present time is complete for the breakdown and formation of glycogen nevertheless the present views afford a clear picture of these processes. This has also led to a much better understanding of the structure and formation of starch and glycogen. (33, 34)

During glycolysis 1,3 diphosphoglyceric acid and enol phosphopyruvic acid give up their phosphate to creatine which stores it as creatine phosphate. Then creatine donates its phosphate bond energy to adenylic acid or adenosinediphosphate for the resynthesis of adenosinetriphosphate and the cycle begins again.

Englehardt (19), Bailey (20) and Needham (21) have shown that the protein myosin is identical with the enzyme adenosinetriphosphatase which causes the breakdown of adenosinetriphosphate supplying the energy for the contraction. These workers were unable to separate the protein from the enzyme activity, and they claimed that myosin and the enzyme were identical. However, it has never seemed to me that this view could be correct. We usually think of enzymes as large protein molecules but not the size and amount as would be the case if the chief muscle protein was at one and the same time the contractile element and the enzyme. There could be no doubt of the close association of the enzyme and myosin, but the possibility that the enzyme was absorbed upon myosin was never shown until recently. Price and Cori (22) have now reported that adenosinetriphosphatase is distinct from myosin and also that it is adsorbed on myosin, so both of the above possibilities are now realized and another brilliant chapter in the chemistry of muscular contraction is becoming clearer.

In spite of much evidence to the contrary many biochemists and clinicians still believe that the creatinine coefficient has much physiological significance. Creatinine excretion is supposed to represent the best index of muscle metabolism. The creatinine coefficient has been calculated for children and adults suffering from the different myopathies to see if, by this means, one may not be able to calculate the amount of functional muscle tissue remaining in the patient. This would be a very interesting and important diagnostic criterion if the creatinine coefficient had any physiological significance. Before applying this line of reasoning, however, to the myopathies let us consider our last investigation of this subject.

145 rats varying in body weight from 50 to 400 gms. were used. The muscle, body and skeletal weights were determined for each animal together with the per cent muscle creatine and the total creatine content of the entire musculature together with the daily creatinine excretion. (23) These rats possessed on the average 44 per cent of their body weight as muscle weight, 8.6 per cent as skeleton (ribs, skull and bones), 0 2 per cent as total muscle creatine and each rat excreted 11.35 mg. of creatinine daily. It is of much significance to this discussion to remember that a 50 gm. rat excreted the same amount of creatinine as a 400 gm. rat, or one weighing 8 times as much.

The correlation coefficient, $r$, between body weight-total muscle creatine; body weight-skeleton; skeleton-muscle weight; muscle weight-total muscle creatine, and muscle weight-skeleton, ranged from 0.7 to 1, and each has a high degree of significance. Also the prediction equations in most of these cases gave values which agreed closely with the observed values. From this data it was also calculated that the muscles of man would contain 118 gm. of creatine which agrees with chemical analysis of human muscles showing 117.5 gm. of total creatine, etc. It is also generally believed that the muscles of man constitute about 40 per cent of the body weight and our prediction equation gives this value as 37-39 per cent in the case of the cat, dog, rabbit and man. (23) No correlation whatever was observed between the excretion of creatinine and any of the above measurements.

Let us now apply this line of reasoning to the myopathies. Hoagland *et al.* (24) studied 49 boys about 10 years of age suffering from progressive muscular dystrophy. They used 5 normal boys of the same age as controls. Data are given for 6 cases to represent different degrees of severity of the disease. They were not inclined to attach much importance to the creatine excretion but used the creatinine coefficient instead. They fed the boys on a high protein diet and this in itself would lead to increases in creatine and creatinine excretion. To this must also be added the phy-

siological creatinuria in boys of this age. It was stated that the creatinine coefficient calculated for the normal boys agreed closely with the correct value reported in Hunter's monograph. (25) But this value, 21.6, is a creatinine coefficient of the normal adult and one is at a loss to understand how they arrived at this figure. It is about 200 per cent above Hunter's figures for a 10 year old boy. Hence they are not justified in using this coefficient for their normal boys.

The data listed in Table 1 below give Hoagland's data and reasoning in regard to the diagnostic value of the creatinine coefficient.

TABLE 1
(Data of Hoagland, *et al*, (24)

| Subjects | | Creatinine Coefficient | Muscle Weight on Body Weight | Muscle Weight |
|---|---|---|---|---|
| | | *mg/creatinine/kilo/day* | *per cent* | *per cent* |
| 5 normal boys | | 21.6* | 40* | 100 |
| (10 years of age) | 1 | 18.7 | 34.6 | 86.5 |
| Progressive Muscular | 2 | 13.1 | 24.2 | 60.5 |
| Dystrophy (from least | 3 | 11.6 | 21.5 | 53.8 |
| to most severe case) | 4 | 10.3 | 19.0 | 47.5 |
| | 5 | 10.0 | 18.5 | 46.3 |
| | 6 | 9.5* | 17.6* | 44.0 |

*21.6 : 40 :: 9.5 : x = 17.6, etc.

At first sight these calculations seem very impressive in showing, based upon calculations of the normal creatinine coefficient (?), that only 17.6 per cent of the body weight is present as muscle tissue in No. 6 the most severe case. Now let us compare this line of reasoning against similar data for the rat, which however, is not suffering from muscular dystrophy, but at the same time a 50 gram rat weighs 8 times less than a 400 gm. rat and these comparisons are, therefore, justified on a body weight basis. (Table 2).

From this data it is seen that our average rat weighs 224 gms., excretes 11.35 mg. of creatinine daily, and this gives a creatinine coefficient of 50.6 (1000/224 x 11.35). This coefficient actually corresponds to 44 per cent of the body weight as muscle weight. To compare this to a smaller rat of our group, say the average of the smallest group, 79.9 gms., we get 11.55 mg. creatinine excretion, corresponding to a creatinine coefficient of 144, which, using Hoagland's calculation above, would give us 125 per cent of the body weight as muscle weight. Instead of this impossible figure for this small rat we found that his muscles, on the average, amounted to only 39.4 per cent of his body weight. It must be remembered that these are actually determined values and not suppositions or calculations, etc.

According to Milhorat (14) the chief difficulty in attempting to estimate how much muscle tissue is present in the myopathy patient, is due to the fact that various amounts of fat may be substituted for muscle tissue, as is sometimes the case in pseudohypertrophic muscular dystrophy. The atrophic fibers may also be replaced by connective tissue. Also in progressive muscular dystrophy the diseased fibers may present variations in size, shape and structure and the muscles may show considerable impairment in function without demonstrable diminution in their total muscle mass. Therefore, while patients with the greatest reduction in creatinine output may have considerable amounts of muscular wasting, the diminution in creatinine output is sometimes greater than the apparent reduction in muscle mass would indicate.

Milhorat, *et al*, (14) are inclined to lay more stress on the creatine excretion in the dystrophies than on the creatinine output. Their findings may be summarized as follows:

| Myopathy | Creatine excretion *mgs.* | Creatinine excretion *mgs.* |
|---|---|---|
| Myasthenia gravis | Not altered | May be low |
| Myotonia congenita | No creatinuria | No change |
| Myotonia atrophica | Creatinuria | No change |
| Progressive muscular dystrophy | Creatinuria | Creatinine retention |
| Progressive muscular atrophy | Creatinuria | Some creatinine retention |
| Amyotonia congenita | Creatinuria | Abnormally high creatinine retention |
| Amyotrophic lateral sclerosis | Creatinuria | Creatinine retention |
| Pseudohypertrophic muscular dystrophy | Creatinuria | Some creatinine retention |
| Paramyoclonus multiplex | Slight creatinuria | |

Before discussing the possible clinical significance of these findings a few statements about creatinuria must be made. Creatinuria, *per se*, is by no means diagnostic of diseases of the muscles, as it occurs in a number of conditions not related to the muscles at all. (3) Creatine is also excreted in starvation and in carbohydrate depri-

vation. In both conditions glycolysis is at a minimum and little or no phosphate (bond energy) is liberated to hold the creatine in the muscles. The creatine then finds its way into the urine. (4) The water and protein intake of the patient must also be known as increases in the intake of either of these will increase the creatinuria. It is also well known that the myopathy patient can form creatine in a normal manner, showing that his liver and kidneys are functioning properly, but he cannot *utilize* this newly former creatine in his muscles. For this reason we believe that the emphasis should be shifted from creatinine-body weight, muscle mass, muscle weight, etc., to creatine, phosphate and carbohydrate metabolism in these conditions.

Why is creatine usually excreted in the myopathies? It was first thought that the creatinuria was due to a liberation of the creatine from the disintegrating fibers. This theory has long since been discarded. The second theory is that of Milhorat, et al (14), who stated that muscle function decreases parallel to the decrease in creatinine excretion and that creatinuria and creatine tolerance represented the mass of improperly functioning muscle rather than the amount of wasted muscle.

Let us consider a myopathy patient weighing 70 kilos. If he were a normal individual this would probably be his average body weight and 40 per cent of this, or 28,000 gms., would be present as muscle tissue. Now let us further suppose that 20 per cent of his muscle tissue, or 5,600 gms. was nonfunctional. According to Milhorat this would require 5,600 x 0.004 or 22.4 gms. of creatine to be excreted into the urine. The patient, however, would never excrete more than about a gm. of creatine in the urine per day. It is also known that 1 gm. of creatine excreted into the urine will equal about 238 gm. of muscle tissue. (23) Milhorat's patients excreted on the average 0.42 gm. creatine daily. (14) This represents 0.42 x 238 = 100 gm. of non-functioning tissue which is only 0.4 per cent of the 28,000 gms. muscle tissue present in a normal individual. It is, therefore, obvious that the creatine excretion cannot measure the amount of nonfunctioning tissue remaining in the patient.

Let us now forget about the *amount* of muscle tissue present. Bloch, Schoenheimer, and Rittenberg (26) showed that the rat synthesized 2 per cent of the total body creatine daily. If it is justifiable to apply this calculation to man we would have 118 x 0.02 = 2.36 gm. of newly formed creatine which, due to a possible derangement in sugar and phosphate metabolism, is then excreted into the urine. Our view, which might be suggested as the third theory of creatinuria in the myopathies, is that the amount of creatine excreted daily by the patient has no relation to the amount of wasted or nonfunctional tissue at all but simply represents that amount of newly formed creatine which is not stored and utilized in the tissues, facts which are well known in this type of patient.

Milhorat's patients excreted 0.42 gm. creatine daily and ours (27, 28) 0.51 gm. These amounts represent 18 and 22 per cent, respectively, of the 2.36 gm. of newly formed creatine.

In the creatine tolerance test the patient ingests 1.32 gm. of creatine and the creatine retention and excretion are determined. The significance of this test is supposed to be analogous to the glucose tolerance test in the diabetic. In fact the myopathy patient may be somewhat diabetic to creatine. But the dose here is only about 1 per cent of the total body creatine and creatine excretion varies widely after its ingestion (3). The creatine which does not appear in the urine simply disappears, or is oxidized by the *creatine oxidase* in the tissue. We believe that the test is simply a creatine oxidation test and as such has little clinical significance. (29)

The excretion of creatine, however, does possess definite diagnostic and prognostic significance in the myopathies, but not in the sense accorded to it by Milhorat. Tripoli and Beard (27, 28), studied 51 cases representing 12 different types of myopathies for a period of 3 to 4 years following glycine ingestion. Those cases classified as primary myopathies of the dystrophic type, in which the average creatinuria following glycine administration increased from 50 to 200 per cent above normal and then later disappeared, showed both subjective and objective improvement. Certain neuromuscular conditions (atrophies) which showed about the same increase and decrease in creatine excretion, however, showed little clinical improvement. In some of these cases the downhill progress of the disease appeared to have been stopped. Cases in which no creatinuria occurred (less than 50 per cent above

TABLE 2
(Data of Beard (23)

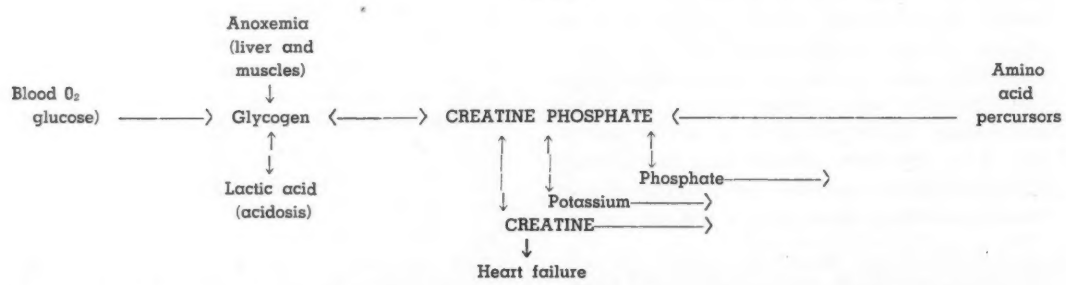
| Group No-Body Weight | | Average Body Weight | Average muscle weight on body weight | Creatinine excretion |
|---|---|---|---|---|
| | *gms.* | *gms.* | *per cent* | *mg/day* |
| 1 | 50-100 | 79.9 | 39.4 | 11.55 |
| 2 | 100-150 | 134.9 | 44.3 | 9.90 |
| 3 | 150-200 | 180.9 | 46.8 | 11.55 |
| 4 | 200-250 | 224.3 | 46.0 | 9.90 |
| 5 | 250-300 | 267.7 | 45.0 | 9.30 |
| 6 | 300-350 | 312.7 | 46.4 | 14.50 |
| 7 | 350-400 | 369.8 | 40.0 | 13.50 |
| | Average | 224.3 | 43.9 | 11.35 |

the control level) or if this increase did not disappear, showed no clinical improvement from the amino acid administration.

It is obvious that no treatment will be effective if the muscle fibers have reached the fibrotic state. It should be remembered that the patient has been developing his disease for some time (1 to maybe 20 years) and that amino acid administration should be continued indefinitely and *a high protein diet should be ingested at the same time,* if any clinical benefit is to be obtained. The sooner glycine administration is begun after the diagnosis is made the better will be the clinical results. One of our cases was a young woman suffering from infantile paralysis for about 2 years. Her right leg was in a brace and the strength in both legs was diminishing. Administration of glycine and a high protein diet for 2 years improved her strength. She was able to walk 2 blocks without her crutches before tiring. We would like to suggest that the myopathies be given glycine with calcium glycerophosphate, then the creatine formed will have extra phosphate to hold it in the muscles (4), and the patient should show the most benefit from this type of therapy. Any inorganic phosphate however, may be given instead of the calcium salt.

The creatine content of the human heart is slightly less than one-half that of the skeletal muscle. The total phosphorus is about the same as that of the muscle but a much greater part of it is present in the acid soluble fraction. Myers and Mangrum (30) and others have established the creatine content of normal hearts and of those that have failed. The normal value is 170 mg. per 100 gm. The results of analyses of many different workers (3) show that in the failing heart, creatine, potassium, and phosphate are *below* normal. Hermann and Dechard (31), who have made extensive studies of this question in the dog and man, are unwilling to correlate the anatomical findings at autopsy with the nature of heart failure and Hermann (9) in his latest monograph on the subject has offered the following scheme to illustrate myocardial failure in terms of physiological chemistry.

TABLE 3




(After Herman G. Synopsis of Diseases of the Heart. C. V. Moseley Co., St. Louis, Mo. 2nd ed., 1941)

Hermann illustrates the above scheme as follows:

"Anoxemia disturbs the biochemical reaction of glycogen, creatine phosphate, creatine and lactic acid metabolism, which are very closely associated in muscular contraction, tone and efficiency. It is assumed that creatine phosphate functions in heart muscle as it does in skeletal muscle in supplying energy for the resynthesis of adenosinetriphosphate. The inability of the anoxic skeletal muscle and liver to resynthesize lactic acid to glycogen causes this acid to accumulate in the blood stream with resulting acidosis. The anoxemia further causes a loss of potassium and creatine which is shown by analysis of mammalian and human hearts that have failed. This tends to produce a vicious cycle which would explain the progessive nature of heart failure. The loss of buffering base (and creatine, which can serve to neutralize lactic acid (HHB) from the tissues results in the inability to acquire the normally large oxygen debt. This causes an increased permeability of the capillary wall and edema results. The precursors of creatine (i.e. glycine) creatine phosphate, or its potassium salt, and glycogen, as methods of combating anoxemia may someday be found to stay the progress of the failing heart."

When it is considered that the creatine content of adult muscles is only about 0.4 per cent and of the heart 0.17 per cent, once again we see the great importance in health and disease of what the late Professor Mendel of Yale called "the little things in nutrition" even though he had the vitamins and inorganic salts in mind at the time.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*"Modern Pothecarias taught the art*
*By doctor's bills to play the doctor's part,*
*Bold in the practice of mistaken rules."*

—*Alexander Pope*

*"We are afflicted by what we can prove,*
*We are distracted by what we know."*

—*Kipling*

# Alumni News

1927—Dr. Irving W. Salowitz was reelected President of the Hancock County Medical Association at its January meeting at Carthage, Illinois. This is the third consecutive term as head of the Medical Society for Dr. Salowitz. The Quarterly congratulates him on his excellent work.

1932—Dr. Felix R. Baylin has returned to the practice of medicine at his former offices, 2660 N. Milwaukee Avenue. Dr. Baylin was recently discharged from military service.

1935—Dr. Louis I. Greenspon was a recent visitor at the school. After three and a half years of military service, Dr. Greenspon has reopened his offices at 161 Halsted Street, Chicago Heights. Good luck from the Quarterly, Dr. Greenspon.

1937—Dr. Meyer Mandel announces his return from military service and the resumption of practice at 909 East Speedway Blvd., Tucson, Arizona.

1939—Dr. Irving Blumenfeld, recently discharged from the Army Medical Corps was a welcome visitor at school. Dr. Blumenfeld is now taking a post-graduate course in Pediatrics and intends to return to New York for the practice of medicine on completion of the course.

1940—The Quarterly was happy to learn that Dr. Lee Gladstone is returning to his practice of general medicine and surgery in McHenry, Illinois.

Dr. Fredrick Spector has opened offices for the practice of general medicine and surgery at 1173 Eastern Parkway, Brooklyn, New York. Good luck from the *Quarterly,* Dr. Spector.

Dr. George C. Markoutsas, who was recently discharged from the service, visited the school recently and informed us that he has opened offices at 8 North Ogden Avenue. During his service as a Captain in the Medical Corps, Dr. Markoutsas received the "Legion of Merit" award for exceptionally meritorius conduct in the performance of outstanding services in the Dalmation Islands of Jugoslavia and in Italy from January to December 1944. He participated in two amphibious raids with British Commando Units and Jugoslav partisans and in spite of tremendous difficulties administered admirable medical service to an overwhelming number of casualties.

When not engaged in actual operations, Dr. Markoutsas was unstinting in devoting his time to the care of the inhabitants and the partisans on the Island of Vis. These people soon grew to revere Dr. Markoutsas not only to his own glory, but to the good reputation of the Armed Forces. Returning for the Island of Vis, Dr. Markoutsas trained medical technicians who took part in raids into Greece. "His courage, zeal, determination, devotion to duty and personal unselfishness reflected great credit upon himself and the Armed Forces of the United States."

We were also glad to hear that Dr. Miles Cermak has returned from military sevice and has opened a new office at 5544 W. 25th Street, Cicero, Illinois.

1941—Major Leo Delno Richey and Captain Thaddeus J. Fijalkowski were recent visitors at school. Both Doctors are on terminal leave after serving in the South-Pacific Campaigns.

Major John M. Staron of Chicago, who has been a patient at the Schick General Hospital for the past seven months, is now on terminal leave and will soon resume practice. Dr. Staron served overseas for twenty months and received the Bronze Star for meritorious service against the enemy in the Philippine Islands. "Major Staron's initiative, aggressiveness and leadership under extremely hazardous circumstances, enabled our casulties to be effectively treated and promptly evacuated."

Major Staron's medical unit was commended by the Commanding General and received the Meritorius Service Unit Plaque. Besides the Bronze Star, Major Staron wears the Combat Medical Badge, Asiatic Pacific ribbon with three battle stars, the bronze arrowhead, the Philippine Liberation ribbon with one star and the American Theatre ribbon.

1942—Captain Abraham Schwartz is now a patient at the Fitzsimons General Hospital, Denver, Colorado. We wish him a speedy recovery.

The *Quarterly* is happy to announce that Dr. Harry M. Siegel has returned from military serv-

ice and has opened offices at 2374 Lincoln Avenue, Chicago, where he will engage in the practice of general medicine and surgery.

Dr. James C. McNamara, after serving with the Paratroopers where he earned numerous citations, has opened offices for the practice of general medicine at 6590 N. Sheridan Road, Chicago. Good luck, Dr. McNamara.

Captain Irving Blumenthal was recently awarded the bronze star for heroic achievement at Zamami Shima, Ryukyu Islands, in August. As Battalion Surgeon, Dr. Blumenthal crossed a dangerous mine field to treat twenty-five men whose truck had plunged over a cliff into the mine fields. After aiding in the evacuation, Captain Blumenthal worked throughout the night rendering medical care and attention to the wounded. Good work, Dr. Blumenthal.

1943—Dr. Jerome S. Tobis, S.A. Surgeon (R), United States Public Health Service is Medical Director of the State Fever Therapy Unit, a division of the Mississippi State Hospital. Dr. Tobis writes that he was recently promoted and expects to be discharged from the service in the fall.

Dr. and Mrs. A. H. Barasch announced the birth of their daughter Ida Louise (5 lb.—10 oz.)

(*Continued on page* 36)

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## ALUMNI RECENTLY SEPARATED FROM SERVICE

| *Class* | |
|---|---|
| 1926— | Quinn, H. Edmond |
| | Larrain, Abel R. |
| 1935— | Mastrianni, Dominick T. |
| | Sklar, Isidore A. |
| | Halperin, Jacob |
| | Paul, Marry M. |
| | Rothenberg, Morris |
| 1939— | Schmidt, William B. |
| | Blumenfeld, Irving H. |
| | Pilchman, Samuel |
| 1940— | Berlin, Louis |
| | Gladstone, Lee |
| 1941— | Staron, John M. |
| | Ziegeler, Rudolph W. Jr. |
| 1942— | Siegel, Harry |
| | Dubrow, Benjamin |

## BOARD OF TRUSTEES

Dr. S. R. Bazell

Dr. S. R. Bazell has joined the roster of the Board of Trustees of The Chicago Medical School.

Dr. Bazell was born in Braddock, Pennsylvania. He received his B.A. from the University of Illinois, and his M.D. from C.M.S. He is now a member of the Chicago Medical Society; Illinois State Medical Society; and the Chicago Society of Industrial Physicians and Surgeons, and various fraternal orders.

In 1942 Dr. Bazell left for the wars and actively participated as a Major in the invasion of the Marshall Islands, Mariana Islands, and the Philippines. He was active in the 36th Field Hospital attached to the 77th Infantry Division. Major Bazell's awards include four medals and three battle stars.

The Chicago Medical School is proud to add the name of Dr. S. R. Bazell to our Board of Trustees.

# Faculty Notes

Dr. Piero P. Foa, Dr. Jay A. Smith and Harriet Weinstein presented a paper on "The Effect of Insulin on the Phosphorylation of Thiamine." This paper was presented at the March 11th meeting of the American Physiological Society in Atlantic City.

Dr. Foa was invited by the Faculty of Physiology to the University Sedes Sapientiae and will lecture under the auspices of the Brazilian-American Cultural Union.

Dr. Foa has recently returned from a trip to Brazil where he visited several institutions in S. Paulo and Rio de Janiero. He delivered the following addresses:

1) Studies on "The Methylation of Nicotinic Acid," at the Instituto Biologico of S. Paulo.

2) "The Effect of Insulin on the Formation of Cocarboxylase," at the S. Paulo Biological Society.

3) "Physio-pathology of Hypertension," a course of five lectures at the Faculty of Medicine of the University of S. Paulo.

Dean John J. Sheinin and Professor Edgar D. Congdon attended the Meeting of the American Association of Anatomists which was held at Western Reserve University, School of Medicine, April 4, 5 and 6. Professor Congdon presented a paper on "The Gross Structure of the Subcutaneous Layer in the Anterior and Lateral Trunk of the Male as Shown by Razor Cuts."

Professor Albert F. Rosenblum has returned to active teaching after a leave of absence of three years while in military service.

Professor Peter Gaberman, who was on leave of absence for three and one-half years, has also resumed his activities on the teaching staff. Professor Gaberman participated in many of the battles in the Pacific Theater of Operations.

We heartily welcome the return of Professors Rosenblum and Gaberman.

Professor Maurice Oppenheim, head of the Dermatology Department, presented a paper on "Local Sensitization of the Skin to Grenz Rays," at the Society for Investigative Dermatology.

# Social Notes

Doctor E. C. Despotes of the Department of Surgery became the father of a baby boy, Theodore, on June 7, 1946. Our heartiest congratulations to Dr. and Mrs. Despotes on this blessed event.

To the following C. M. S. students who ended their courtship campaigns successfully, we extend our best wishes for the many years to come:

May 18—Arthur Rothenberg (C.M.S. '48) married to Suzanne Susman.

May 30—Marvin Wertheim (C.M.S. '49) married to Evelyn Klein.

June 2—Dudley Neustein (C.M.S. '48) married to Bernice R. Grobstein R. N.

June 8—Jesse Abrahams (C.M.S. '48) married to Gladys Alweiss.

June 16—Arthur Epstein (C.M.S. '49) married to Pearl Bramson.

June 22—Gordon Campbell (C.M.S. '47) married to Ruth Ann Norgren.

June 23—Marvin Brown (C.M.S. '47) married to Lillian Liane Alpert.

June 23—Leon Yorburg (C.M.S. '49) married to Betty Mann.

. . . . .

# Obituary

We deeply regret to announce the sudden death of Dr. PAUL GEORGE PAPSDORF. Doctor Papsdorf was graduated from The Chicago Medical School in 1922, and served on the faculty from 1930—1938 as Associate Professor of Oral Surgery. In 1938, ill health forced his retirement from the teaching staff.

Doctor Papsdorf was a very active alumnus, serving as the Alumni Representative on the Board of Trustees as well as Secretary of the Board for a number of years. He was also a fellow of the American Medical Association and served as Vice-President of the American Society for the Advancement of General Anesthesia.

In Dentistry, Doctor Papsdorf served also as Vice-President of the Medical and Surgical Staff of Evangelical Hospital.

The Chicago Medical School and the medical profession have suffered a great loss by his passing.

## — CLASS HISTORY —

The Chicago Medical School class of 1946 came into existence in June 1943. American and British planes were bombing Berlin, the Russians were fighting the Nazis to a standstill on the Eastern Front, and the United States Navy was island-hopping in the Pacific. Amidst this insecurity of war the American nation was reaching its highest level of productivity, not only in materials, but also in men. Medicine was fighting an all-out battle for victory, and the Chicago Medical School had dedicated itself to the service of its country. The Freshman class in June, 1943, entered upon an accelerated program with the determination and ideals so common to the students of our school.

The class settled itself in Chicago, became acquainted with the city and became part of its life. It grew slowly, taking shape under the able hand of the faculty.

By the time the Freshman year was over the students had developed a confidence in themselves and in their school and a strong desire to make a place for themselves and the school in the medical life of the nation.

While sophomores, the class began to organize and chamelize its attempts to improve the school. Through its instigation, the other classes joined it in joining a student council, the main purpose of which was to provide the school with an endowment fund. The Endowment Committee was formed for this purpose. This committee, in co-operation with the Dean, raised over $300,000 from the students and their families alone.

By this time the class was in its third year, it was 1945. The war ended both in Europe and Japan. Clerkships began. The class was split up into 3 parts for the junior program. Dr. Krumholz died and the class felt his loss keenly.

The clinics were a new matter to the class. The patient was nothing like a cadavre. The social aspect of medicine, the personal relation between physician and patient, began to acquire increasing importance. The class mastered this step and moved on.

Internships — A mad scramble. Disappointments following hope and finally joy. Sometimes it was a long time before the joy.

The Senior year started in fall, 1945. The class felt the beginning of the end. After Christmas, comprehensives began — the last long grind. Chemistry, Physiology, Pathology, Bacteriology, and all the other names which sounded so far back in the preclinical years. There was the realization that NOW was the time to really learn them again, the last chance in medical school to review them.

The last spring was the longest one. The second day of summer brought an early June day for Commencement. The class filed in with the procession, listened to the speeches, walked up to receive the diplomas, switched the green tassel to the right and as it walked down the steps from the speaker's pedestal it was walking out of the building, out of the street, out of the city to which it had come three hard years before.

* * * * *

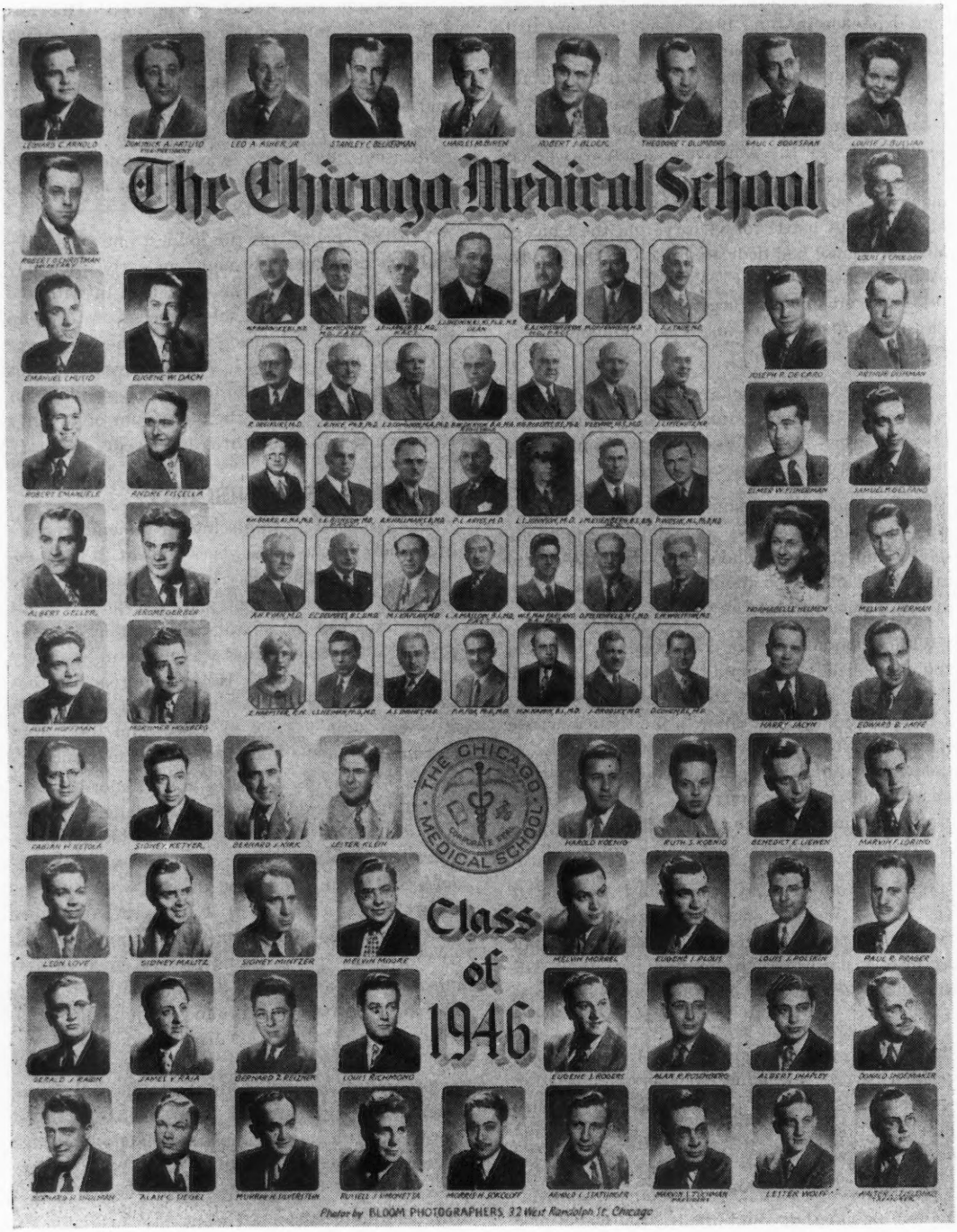
## REMINISCING

This is strictly reminiscing. I remember some high spots of the three years I spent in Chicago. I remember the first day in School and how the Dean looked, though not what he said. I went home, practiced the anatomical position for three days. No one knew what was flying in histology until it was all over. How I approached that cadaver the first day — didn't even touch him, although later I grew to know him intimately and loved him for his patience and tolerance.

The study of medicine is always more than a collection of essential facts, for while medicine is a science, its practice is an art. Students require a mellowing such as bonded whiskey undergoes (I sometimes feel as if I were aged in wood). It is a matter of living with Aeschylus long enough to have him become an essential part of you. It is a liking for the smell of disinfectant and anesthesia, an appreciation for the way busy nurses run around hospital floors, a desire to read all the medical books and magazines in all the libraries. It is a liking for sick people and a sympathy for them—the ability to listen, look with interest, kind hands, soothing words. It is a deep humbleness before the phenomenon of human living.

Since this is the last time I shall write in the *Quarterly* as a student, I want now to thank all

(*Continued on Page* 21)


The Chicago Medical School
THE CHICAGO MEDICAL SCHOOL
Class of 1946
Photos by BLOOM PHOTOGRAPHERS, 32 West Randolph St. Chicago

# Commencement

The thirty-second annual commencement of The Chicago Medical School took place on June 22, 1946, at The First Congregational Church, Washington and Ashland Blvds., Chicago, Illinois. Sixty graduating seniors participated in the exercises which represented a culmination of three years in medical school under an accelerated program. The Reverend Edwin W. Todd, D.D., opened the exercises with a most appropriate invocation, praying that the graduates would retain and cherish the hallowed ideals of their profession. The Reverend James M. Yard, D.D., Director, Chicago Round Table of the National Conference of Christians and Jews, then gave a brilliant address to the graduating class and members of the audience. He concerned himself with the idea that in the search for a better world the physical scientists have unloosed a devastating force capable of the destruction of man's world and unless the social scientists throw themselves unhesitatingly into the struggle to improve human relations, this destruction would almost certainly take place. Doctors, he said, are social scientists, and their part in the job is important. Psychiatrists could be valuable adjuncts at meetings of international diplomats, preventing individual idosyncracies from barring the necessary understanding between nations.

After the address, Dr. John J. Sheinin, Dean of The Chicago Medical School, presented to Dr. John C. Evans, Vice-Chairman of the Board of Trustees, the candidates for the degree of Bachelor of Medicine. The degrees were individually conferred by Dr. Evans. The program ended with a benediction by Dr. Todd.

The program follows:

Prelude—"Pilgrim Chorus" .....Wagner

1. The Commencement Procession
   Processional—"Marche Sollenelle" Lemaigre
   The Marshall
   Candidates for Degrees
   Faculty
   Officers of the Alumni Association, Trustees, Administrative Officers, and Guests
   Commencement Chaplain
   Chairman, Board of Trustees and Commencement Speaker
2. The National Anthem—
3. The Invocation—
   Prayer by the Commencement Chaplain,
   The Reverend Edwin W. Todd, D.D.
4. Commencement Address—
   The Reverend James M. Yard, D.D.
   Director, Chicago Round Table of the National Conference of Christians and Jews
5. Presentation of Candidates for the Degree of Bachelor of Medicine
   Dr. John J. Sheinin, Dean
6. The Conferring of the Degree of Bachelor of Medicine
   Dr. John C. Evans, Vice-Chairman, Board of Trustees
7. Statement from the Board of Trustees
   Dr. John C. Evans, Vice-Chairman, Board of Trustees
8. The Benediction
9. The Recession ..... Coronation March

* * * * *

## REMINISCING—

(*Continued from Page* 19)

the members of the staff that I worked with for three years. Sid Malitz and Wally Salzman, my successors; Gene Plous and Sandy Peckler, my business managers; Arny Statzinger and Gene Rogers, my hard-working associate editors; Marv Lerner, my photographer; Norma Helmen and Shep Shapley, my artists; Manny Chusid and Sherwin Isaacson, my book reviewers; Don Shoemaker, my typist; Lenny Tilkin, for advice; the many other members of the various departments of the staff—all the hard workers; and last but far from least, my mentor and friend, Burt Rockliff.

I've made enough enemies, so it's time to stop. I never liked my classmates half as much as I did that Saturday morning we swung the tassels to the right. I even wanted to kiss Dr. Sheinin, I was so happy. Under the mellow influence of the night before (not to mention the mellowness of the next few days), I took to heart Dr. Todd's closing remarks, "Go in peace. Remember the poor. Be gracious and tolerant to one another."

Amen.

*B. Shulman*

# A FEW THOUGHTS ABOUT SYPHILIS

Maurice Oppenheim, M.D.
*Professor of Dermatology and Syphilology*
*The Chicago Medical School*

THE relation of syphilis as an infectious disease to the other infectious diseases of the human race is peculiar, not only because it is not analagous to acute or chronic infections (since it combines an acute and a chronic stage with a latent period in between), but also because it has no true immunity. Other infectious diseases like measles, variola, etc. usually heal with complete immunity, and with a total absence of the infecting agents. Chronic infectious diseases like leprosy and tuberculosis have no immunity in the true sense of the word, because the bacteria causing these diseases are present somewhere in the organism. Syphilis is similar to this in that reinfection is only possible after complete healing has occurred. As a matter of fact, this is the only true proof of healing, for continual negative sero-reactions and absence of symptoms for a long period of time are no absolute indication of healing. If syphilis is not healed, we know that the *Treponema pallidum* is located somewhere in the body and that some immunity is present. But a relapse is possible at any time, occurring if the immunity should decrease or if the virulence of the *Treponema pallidum* should increase, or if a hypersensitivity to the organism were to develop (i.e., gumma of the skin or of any internal organ).

That actual condition of a syphilitic is determined by the following factors: individual susceptibility, number and quality of Treponema (active, dormant, arsenic-mercury-bismuth-fast, etc.), grade of relative immunity, serologic condition, stage of hypersensitivity, and past treatment.

To illustrate this, a patient presenting a primary lesion will demonstrate no immunity, negative serology, few active Treponema and normal susceptibility. A patient possessing a generalized rash on the skin will present many active Treponema, highest immunity, and 100% positive serology. High immunity, few inactive Treponema, 50-60% positive serology are indicative of a latent stage while high immunity, few active Treponema, and hypersensitivity indicate a gumma. (Tertiary stage)

It is not yet definitely decided whether or not a dormant form of *Treponema pallidum* exists. The immunity which begins with the appearance of the primary lesion (hard chancre) increases with the appearance of the generalized eruption weeks later, or 9 weeks after initial infection. At this time the sero-reactions are 100% positive. These reactions parallel the degree of immunity of the individual, but bare no relation to the number of organisms present. Thus a comparative decrease in immunity accompanied by an increase in activity and number of Treponema cause the skin relapse.

The body reacts against the Treponema, not by phagocytosis or leucocytosis, but by the increased production of plasma cells, which provide the source of the immune bodies. Therefore, we do not find much increase in the polymorphonuclear leucoytes in the blood except for that short period during the cutaneous generalized eruption, unless fever, malaise, fatigue, and other symptoms of an acute infectious disease also develop. This period, which we call the prodromal stage, is similar to other acute infectious diseases and occurs at the end of the eighth and the beginning of the ninth week after the infection. At this time, the *Treponema pallidum* which is most abundant in the lymphatic nodes and vessels, begins to enter the general circulation through the thoracic duct. It is now that the fate of the syphilitic patient is determined.

The spirochaetes settle mostly in the skin and mucous membranes, then in the internal organs, especially the liver, spleen, lungs and kidneys (parenchymatous organs), and in the various systems of the body (blood vessels, bones, nervous system, etc.). At this time almost half of the patients have a positive spinal fluid.

And so internal and systemic foci can develop and display manifest symptoms at any time during the life of the syphilitic patient, ten, twenty, or even fifty years after the initial infection. These facts must be kept in mind in the treatment of syphilis.

During the period that I was an assistant to Neumann at the Viennese University Clinic at

the beginning of the twentieth century, the treatment of syphilis consisted only of administration of inunctions of blue ointment containing 33% metallic mercury, and internal doses of mercury (particularly in congenital syphilis of infants and babies). The accepted policy was to wait until the generalized eruption was fully developed for two reasons: 1) To confirm the diagnosis (at this time no darkfield demonstration of the organism was performed); 2) For production of antibodies from the skin which was considered as the most important source of antibodies (esophylactic action of the skin). With this treatment the results were satisfactory. We observed that the proof of complete healing, as always, lies in the fact that these people became reinfected, that gummata rarely appeared, and that even general paresis and tabes dosalis were infrequent. It is an established fact of experience that if the skin is very much involved, the nervous system is less frequently affected, and it was because of this that we waited for the maximal skin manifestations before beginning treatment.

After Professor Neumann retired in 1904, Professor Finger took over the Chair of Dermatology and Syphilology. At this time the new era of syphilis began: first the transmission of syphilis to animals (Metchnikoff and Roux), then the sero-reactions by Wasserman in 1906, and in the same year the discovery of the *Treponema pallidum* by Schaudinn, in 1908 the discovery of Salvarsan (Ehrlich), then the proving of the infectiousness of the gumma and the presence of the *Treponema pallidum* in the brain, in the spine and in aneurysms. The spinal puncture was introduced for the first time. The toxic theory of syphilitic symptoms was no longer held, and the rule was fixed that every syphilitic symptoms was caused directly by the *Treponema pallidum*. Meta and para syphilis were no more. Thus the foundation was laid for the modern treatment of syphilis.

It was proved that the pentavalent arsenical drugs such as Acetarsome and Tryparsamide were trespassing upon the barrier of the central nervous system, whereas the trivalent arsenicals were not. Wagner Jauregg introduced fever therapy in syphilis, first working with tuberculin injections, and then typhoid fever and still later with malarial fever. At that time there were two main methods of treating syphilis: 1) the abortive treatment, and 2) the prolonged chronic intermittent treatment.

In the last few years many techniques have been developed in an attempt to shorten antiluetic treatment, as Ehrlich intended in his "Therapia Magna Sterilisans." The scientists thought that mass infusions of neoarsphenamine or mapharsen could sterilize the organism and destroy all *Treponema pallidum* present. But this method was too toxic, for encephalitis and kidney involvement were frequent complications. Then the one-day treatment was introduced: a combination of high artificial fever with bismuth and neoarsphenamine, but too many deaths occurred. The sulfa drugs were then tried without any positive results. Now we have the Penicillin treatment for syphilis.

Penicillin has a great advantage over the other drugs because of its decreased toxicity, its rapid effect in removing early luetic symptoms. Therefore, it is of great value in the prevention of the spread of this disease. The armed forces used this drug more than any other, because it rendered the patient non-infectious, and the soldier could be returned to active duty in a very short time. The army is now using 4 to 5 million units of Penicillin over a period of ten days. The effect of the arsenicals and the heavy metals is to stimulate the formation of antibodies. It is possible that Penicillin also stimulates the production of antibodies and because of its large dosage the Treponema is destroyed. The same result can be achieved with bismuth, neoarsphenamine and mercury over a longer period. We know that the abortive treatment consists of intensive treatment instituted as early as possible after the discovery of the primary lesion when the serologic tests are still constantly negative. After a single treatment (neoarsphenamine six grams for males, five grams for females and sixteen to twenty injections of bismuth), the syphilis can be cured completely with constant negative sero-reactions, no relapses, no gummata, tabes or general paresis. Many reinfections in patients who were treated in this way have proven the value of this method, and the same holds good for the chronic intermittent treatment performed over a period of three years in cases where the serologic tests are positive from the onset of the hard chancre.

(*Continued on page* 29)

# FENESTRA NOV-OVALIS

Stanley Reichman

In this remarkable era of progress many mechanical devices are seen to aid certain types of deafness in which the inner ear is still functioning. Up until the last decade or so, these instruments were the only means of helping sufferers of otosclerosis. But in 1937 Julius Lempert devised an operation, fashioned after the work of Holmgren and Sourdille, which tends to overcome the effects of the disease, producing a marked improvement in hearing. This difficult procedure has been called the Fenestration or Fenestra Nov-Ovalis, and has been successful in a remarkable number of cases.

Otosclerosis[1] is a disease of unknown etiology (though probably of hereditary predisposition) occurring with an insidious onset, most commonly in females between the ages of twenty and thirty-five. It is diagnosed by clinical and family history, and by certain clinical tests. The morbid anatomy consists of hyperplastic fibrotic and bony changes, primarily of the inner ear capsule, but with sites of predilection corresponding to the normal points of ossification. The results in patients who are operable are such that the organs of hearing of the inner ear remain unchanged, but the normal passage of sound through the middle ear to the inner ear is interrupted by the sclerotic changes. The degree of damage is determined by the use of the audiometer, a device which measures the frequencies of sound waves perceptible to the individual.

Thus in patients who are found to possess obstruction to these sound waves, it is conceivable that with the surgical creation of a new passage for the vibrations, the patient's hearing will become remarkably improved. And this proves to be the case. However, before discussion of the surgical techniques involved, it is perhaps well to review the normal transportation of sound to the organs of Corti as well as certain important anatomical relationships.[2]

Normally, sound vibrations pass through the external auditory meatus to the tympanic membrane, which separates the external ear from the air chamber in the temporal bone known as the middle ear. The middle ear or tympanum is lined with a mucous membrane and may be pictured as a cube, having six boundaries and containing the chain of ossicles: the malleus, incus, and stapes.

The larger part of this middle ear chamber lies opposite the tympanic membrane and is known as the true tympanum. The epitympanic recess is the name given to the remainder of the cavity which extends above the level of the membrane. The recess is continuous behind with the tympanic antrum and communicates through that with the mastoid air cells. Thus it may be noted that the middle ear is accessible by surgical exposure through the mastoid process.

The *roof* of the middle ear is the tegmen tympani forming the anterior surface of the petrous part of the temporal bone. The *floor* separates the cavity from the jugular fossa and is continuous anteriorly with the posterior wall of the carotid canal.

The *posterior wall* is noteworthy in that it presents three important structures: a bony conical projection known as the pyramid, perforated at its summit by the tendon of the stapedius; an opening called the aditus lying between the epitympanic recess and the tympanic antrum; and the posterior canaliculus for the chorda tympani through which the latter (a branch of the facial nerve supplying the anterior two-thirds of the tongue for taste) passes into the tympanic cavity, thence across the tympanic membrane and handle of the malleus, exiting through the anterior canaliculus of the lateral wall.

The *anterior wall* presents two canals lying one above the other, and separated by a thin layer of bone which in its posterior end becomes the process cochleariformis (seen on the medial wall). The upper and smaller canal lying just below the tegmen tympani is the canal for the tensor tympani. The lower is the bony part of pharyngo-tympanic (Eustachean) tube connecting the middle ear with the nasal cavity.

The *medial wall* of this chamber is also the lateral wall of the inner ear, and upon its sur-

1. *Cyclopedia of Medicine, Surgery, and Specialties;* Vol. 5, 1943.

2. Cunningham's *Anatomy.* 8th ed.

face is seen the bulge or promontory produced by the first coil of the cochlea on which lodges the tympanic plexus of nerves. An oval opening, the fenestra ovalis, closed by the base of the stapes and leading into the vestibule of the bony labyrinth is situated above the promontory. An elevation, the prominence for the canal of the facial nerve, can be found above the fenestra and below the bulge produced by the external semi-curcular canal. An irregular opening lying below the promontory and partially hidden is the fenestra rotunda which communicates with the scalar tympani of the cochlea and is closed

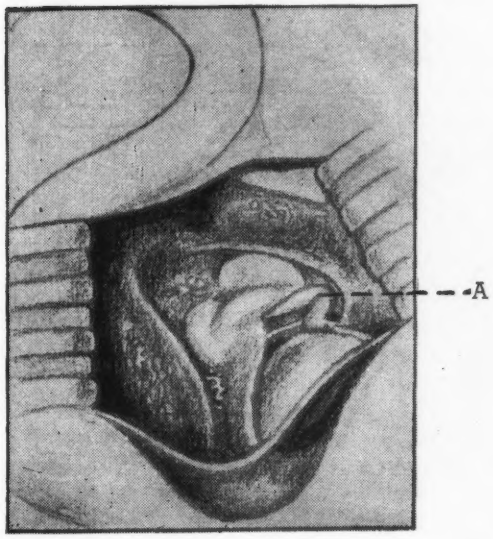



Fig. 1—(AFTER LEMPERT) shows medial wall of middle ear cavity as viewed from tympanic antrum. The mastoid cell structure has been removed, the incudo-malleolar joint, *A*, is visible as well as the sharp prominences of the three semi-circular canals. The tympanomeatal membrane has also been created.

by a secondary tympanic membrane. Another structure, seen on this wall, already mentioned, is the process cochleariformis, the posterior bony end of the lamella of the partition between the Eustachean and tensor tympani canals, which forms a pulley over which the tensor tympani muscle plays.

The ossicles vibrate sympathetically with the tympanic membrane, thus transporting the sound vibrations from the lateral wall of the tympanic cavity to the medial wall. The ossicles are three bones: malleus, incus, and stapes, often likened to hammer, anvil, and stirrup, respectively. The first and largest of these proceding medially is the malleus possessing a handle, a neck, head, and two processes. The handle is fixed to the medial surface of the tympanic membrane, the head and neck being situated in the epitympanic recess. The head of the malleus is connected to the body of the incus by a synovial joint, the incudo-malleolar joint. This "hammer" is also attached to the walls of the tympanic membrane by a series of ligaments: the anterior, superior, and lateral ligaments. The incus has a body and two processes, and is connected at the lentiform nodule with the head of the stapes, from which arises a neck, two limbs, and a base attached to the fenestra ovalis.[3]

The internal ear is composed of a series of bony labyrinthine passages within the petrous portion of the temporal bone, each in itself containing membranous labyrinthine passages. The bony labyrinth is composed of the cochlea (containing the membranous duct of the cochlea), the vestibule (containing the membranous chambers: utricle and saccule), and the semicircular canals (containing the membranous semicircular ducts). Within the membranous passages flows a fluid which, though entirely divorced from the lymph system of the body, is termed endolymph. The space formed between the membranous labyrinth and the bony labyrinth contains a fluid known as perilymph, and is completely closed except for a connection with the subarachnoid space through the aquaduct of the chochlea.

When the base of the stapes vibrates against the oval window, the perilymph is set into motion. The latter stimulates the endolymph and the waves pass to the duct of the cochlea. Thus the vibrations, originating at the fenestra ovalis, pass through the vestibule to the scalar vestibuli which in turn communicates with the scalar tympani via the heliocotrema. The fenestra cochlea or rotunda is seen near the vestibule at the beginning of the scalar tympani. It functions for reduction of the endolymphatic vibrations after the organs of Corti have been stimulated. The latter are considered by some as the true organs of hearing, and it is from them that impulses arise to be sent along the cochlea division of the auditory nerve to the auditory area of the cortex where interpretation occurs.

3. (Fixation of the stapes at the oval window is the most frequent type of damage occurring in otosclerosis.)

The semicircular canals are three in number and function for equilibrium. They are connected through the vestibule with the chochlea. There are two in the vertical plane, the superior and posterior semicircular canals, and one in the horizontal plane at 90° to the other two, the lateral or external semicircular canal. Each of these canals opens into the vestibule through an ampullated end, the lateral or external canal opening immediately above the fenestra ovalis and causing an elevation in the medial wall of the tympanic cavity above the canal for the facial nerve.

The principle involved in the operation about to be described may be likened to that of the commonly used hearing aids. The latter magnify the sound vibrations to such a degree that in spite of the sclerotic changes in the middle ear the endolymph is still set into motion. However, if the changes are in too great excess, the mechanical aids are no longer fully effective. The operation, on the other hand, consists of

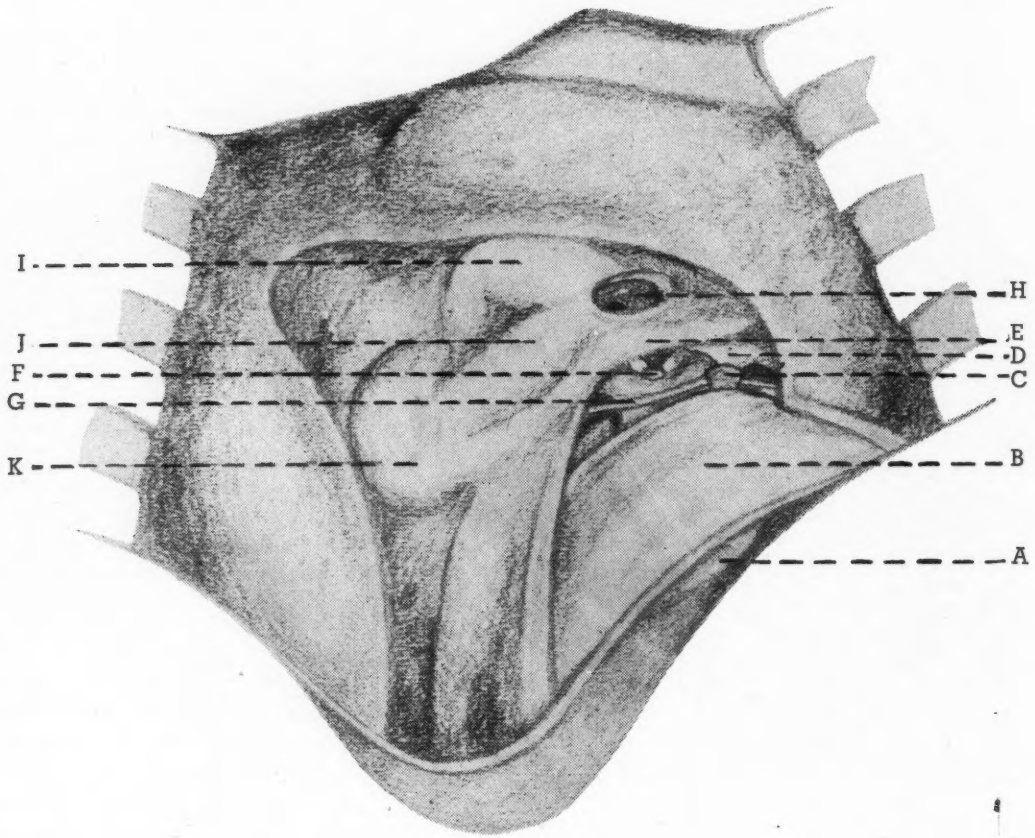



Fig. 2—(AFTER LEMPERT) indicates area of fenestration of vestibule with utricle visible, *H*. The superior, posterior, and supero-posterior aspects of the cutaneous membrane which lines the external auditory meatus is clearly shown through exenteration of the mastoid cell structure. It is the same as the periosteal lined portion of the tympano-meatal membrane, *B*. Below and medially can be seen the lower edge of the drum membrane, *A*. In this illustration the incus and malleus up to the anterior malleolar ligament have been removed thus exposing: *C*, tendon of the tensor tympani muscle; *D*, processus cochleariformis; *E*, prominence for the canal of the facial nerve; *F*, stapes, with base in place at true fenestra ovalis; *G*, chorda tympani branch of the facial nerve; *I*, superior semicircular canal; *J*, external semicircular canal; *K*, posterior semicircular canal.

the surgical creation of a new oval window in the vestibule[4] so that the normal sound vibrations will set the endolymph of the inner ear into motion and stimulate the functioning organs of Corti.

The *technique*[5] itself may be best described by a series of distinct steps in which the surgeon exposes the middle ear, creates the tympanocutaneous membrane, removes the structures in the middle ear which no longer need be present for the passage of sound, i.e., the ossicles, fenestrates the vestibule, and repairs the wound by the membrane he has created in the process.

Exposure of the middle ear is performed in two steps, the *first* consisting of endaural incisions which lay bare the mastoid process, and the *second*, that of a complete, simple mastoidectomy. The latter consists of penetration of the mastoid antrum by removal of the perilabyrinthine cell structure. The approach exposes not only the epitympanic recess, the incus, and malleus, but the sharply defined prominence of the external semicircular canal located on the medial wall of the middle ear. (Fig. 1)

The tympanocutaneous membrane, which is later used to cover the artificial window fenestrated in the vestibule, is created in the *third* step by skeletonizing the superior, posterior, and supero-posterior aspects of the external meatus by exenteration of the mastoid cell structure. This procedure presents the picture of a bony canal without its roof, protected only by the cutaneous membrane which lines it. (Fig. 1)

The *fourth* step, performed in order to bring the ampullated ends of the external and superior semicircular canals into view, consists of the performance of a modified radical operation. The pyramidal eminence, described as lying on the posterior wall of the middle ear, is removed so that the stapes, incus, and chorda tympani branch of the facial nerve are exposed. Next, the incus is removed and discarded by separation of the incudo-malleolar and incudo-stapedial joints. Now also exposed is the posterior half of the roof of the vestibule, the oval window with the stapes in place, and above the latter the promontory for the canal for the facial nerve. The fenestra rotunda and the posterior aspects of the cochlea promontory may also be seen. Next, the head and neck of the malleus up to the attachment of the anterior malleolar ligament are removed thus exposing the entire roof

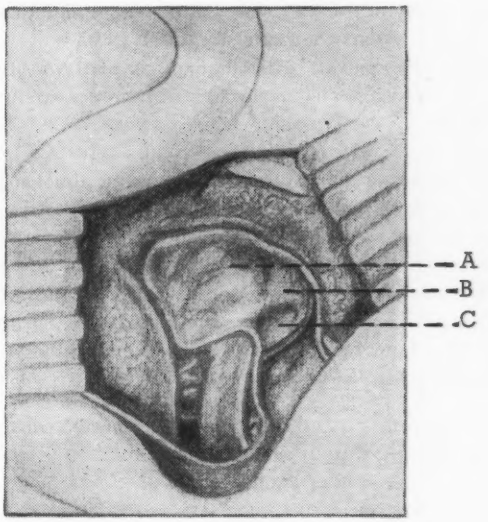



Fig. 3—(AFTER LEMPERT) shows tympanomeatal membrane after flapping. *A*, periostial lined portion of membrane; *B*, upper, flaccid part of drum membrane (Shrapnell's membrane); *E*, remainder of tympanic membrane.

of the vestibule, process cochleariformis, and the tendon of the tensor tympani. (Fig. 2)

The *fifth* step is performed by means of a special polishing burr which fenestrates the vestibule superiorly to the course of the facial nerve and the true fenestra ovalis along the level and just anterior to the prominence of the ampullated ends of the external semicircular canal. The new window has an area of ten sq. mm. and extends down to the endosteal membrane lining the perilymphatic labyrinth. The edges

4. The fenestration was formerly performed in the external semi-circular canal. However, it has been found that fenestration of the vestibule contributes to the patency of the window, not only because of the increase in size of the orifice, but also because of the greater width of the perilymphatic labyrinth at this point. Such is desirable for the prevention of accumulated capillary extravasations which may stimulate fibrotic closure of the window.

5. *Fenestra Nov-Ovalis*—Julius Lempert. Archives of Otolaryngology. Nov. 1941, Vol. 34.

of the window as well as the inner cambium layer of the bony walls of the labyrinth are smoothly shaved in order to prevent bony regrowth and closure of the opening. (Fig. 2)

At this point the bony labyrinth has been fenestrated and the perilymphatic membranous labyrinth is exposed. Fenestration of the later is then performed resulting in exposure of the endolymphatic membranous labyrinth, with the utricle being brought into view.

The fenestration is now complete, and the *last step* consists simply of the repair achieved by flapping back the cutaneous membrane created from the external auditory canal as described above. This flapping is achieved by cone-shaped incisions in the membrane extending from the tympanic ring outward as far as the outer end of the bony canal, allowing for elevation of the cutaneous membrane and backward displacement so that the region of the tympanic air space is sealed by the tympanic portion of the tympano-meatal membrane, the exenterated mastoid region by the periosteum lined meatal portion of the membrane, and Shrapnell's membrane[6] covering most of the fenestrated area. (Fig. 3)

Since this operation has been perfected by Dr. Lempert and performed by him and men who have studied under him, over 5,000 such aural fistulae have been created. There has been no mortality whatsoever, and the success of the operation may be noted in that over 50% of the cases have had their hearing restored to the practical physiological level, and an even greater number markedly improved beyond their previous condition.

The phenomenon of surgically restored hearing is in itself remarkable, but accompanying it as well is the wonderful transformation in the psyche of the patient. The fenestration offers new opportunities for these people in all walks of life, and permits them once again to enjoy and appreciate the pleasant sounds which we all take so much for granted.

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6. Shrapnell's membrane is defined as the thin, upper (flaccid) part of the tympanic membrane, and is used to line the periosteal layer of the fenestra because it possesses an epithelial lined surface. The presence of the latter is thought to discourage the growth of new bone.

## ALLOXAN DIABETES—

(*Continued from page* 8)

by Blatherwick (7). Rats were made diabetic by the administration of alloxan; of these, some recovered spontaneously. Those who recovered were given a 65% carbohydrate diet and diabetes reappeared remaining for as long as 4 months after the diet had returned to normal. Blatherwick concludes that since a high carbohydrate diet can make a latent diabetes flare up, diabetics should avoid the use of too much carbohydrate, their blood sugar should be kept low and their urine sugar-free.

The selective action of alloxan has been utilized by Brunschwig and his collaborators (8, 9, 10) in an attempt to destroy insulin producing cancer cells originating from the insular tissues. A 32-year-old man suffering from 2 to 5 severe hypoglycemic attacks daily despite two previous operations for carcinoma of the pancreas, was treated with 0.6 to 1 g. of alloxan per kilo of body weight. The hypoglycemic attacks were abolished for periods of 10 to 20 days following each course of alloxan injections despite the fact that the patient's blood sugar remained around 30 mg. %. Eventually however the attacks returned despite the administration of alloxan many times greater than those which are lethal for experimental animals. The patient, furthermore, suffered from severe reactions such as chills, vomiting, icterus, fever, anemia and even coma, and it was decided to intervene surgically for the third time. After this operation which revealed diffused metastases of insular tissue in the liver and peritoneum, the patient died. Three other patients with diffuse non insulin-producing carcinomatosis were unaffected by alloxan and their blood sugar remained practically unchanged. It is possible that the discovery of alloxan diabetes may shed new light on the etiology of human diabetes as alloxan has been found in human urine (33, 35) and in normal animal tissues, especially in the liver (51). A derangement of the purine metabolism, perhaps following pituitary disease, may result in an abnormally high production of alloxan and necrosis of the islands of Langerhans.

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## SYPHILIS—

(*Continued from page* 23)

But the main factor remains that unless every *Treponema pallidum* is destroyed, we can expect the damages of late syphilis which mark this disease as one of the most dangerous and devastating to the individual. Therefore, we must consider all of the new rapid methods of treatment as experimental methods. This viewpoint was also held at the convention of the A.M.A. in 1945 by almost all of the authorities. Before we could conclude that neoarsphenamine healed syphilis without any deleterious consequences, we found it necessary to observe the disease for twenty years or more. Therefore, in the interest of scientific accuracy and human welfare, we must wait at least another two decades before we can safely evaluate this new rapid treatment.

It is my opinion that syphilis should be treated individually (not according to a particular schedule) with the old methods of abortive and chronic intermittent therapy. We should leave the modern rapid treatment to the experts in the research centers for further perfection and development.

# NEW ERA IN QUANTITATIVE ABSORPTION SPECTROSCOPY

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*The Chicago Medical School*

A preliminary quantitative separation of the chemical constituents of a biological system before the assay has always been a useless and painful procedure to the biochemist. With the understanding of the basic principles of absorption spectroscopy, a few fore-runners have successfully analyzed biologically-important mixtures containing five constituents without preliminary separation or utilization of numerous reagents.

For example, in the problem of determining the quantity of cytochrome C in mammalian tissue, it was impractical to remove all traces of hemoglobin and myoglobin before assay. Therefore, it became necessary to devise a method to correct for the impurities present.

To clarify the solution of this problem, let us consider the passage of a beam of monochromatic light (figure 1) of incident intensity $I_o$, through a series of three solutions of different constituents with concentrations $c_1$, $c_2$ and $c_3$, whose extinction coefficients are $E_1$, $E_2$ and $E_3$ and whose intensity of transmitted light, after passing through a solution contained in a cell of thickness 1, are $I_1$, $I_2$ and $I_3$, respectively. From the Bouguer-Beer law (see **Quarterly** 4,8-1943) it is seen that

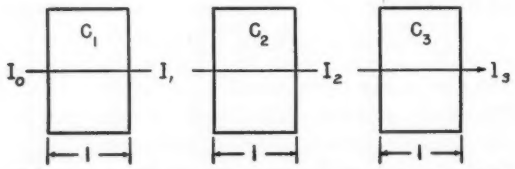


Figure 1. **Transmittance of monochromatic light by three-colored solutions.**

$$\log I_1/I_o = -E_1c_1l;\ \log I_2/I_1 = -E_2c_2l;$$
$$\log I_3/I_2 = -E_3c_3l.$$

By adding these three equations, the result obtained is

$$\log T\lambda x = \log I_3/I_o = -E_1c_1l - E_2c_2l - E_3c_3l,$$

where $T\lambda x$ is the transmission of light at wave length $\lambda x$, after passing through the three solutions.

If $T\lambda x$ is measured at three specfic wave lengths $\lambda_1$, $\lambda_2$ and $\lambda_3$ and the following equations solved simultaneously for any consituent such

$$\log T\lambda 1 = -E_1\lambda_1c_1l - E_2\lambda_1c_2l - E_3\lambda_1c_3l$$
$$\log T\lambda 2 = -E_1\lambda_2c_1l - E_2\lambda_2c_2l - E_3\lambda_2c_3l$$
$$\log T\lambda 3 = -E_1\lambda_3c_1l - E_2\lambda_3c_2l - E_3\lambda_3c_3l$$

as $c_1$, its concentration can be calculated providing the extinction coefficients and cell thickness are known. The general solution of the equations for a particular constituent is

$$c_1 = a \log T\lambda 1 + b \log T\lambda 2 + d \log T\lambda 3$$

where a, b and d are constants easily calculated. The above equations are valid also when the three chemical constituents are in mixture if there is no interaction.

When a large number of assays are contemplated, as in the clinic, in a series of systems, differing only in concentration, the simplest solution of the above equation is by an alignment chart. As yet this solution has not been applied in other laboratories in America.

The fundamental principle, involved in the construction of an alignment chart, consists in the representation of an equation by means of scales in such a manner that the equation is satisfied. An alignment chart is a nomograph whose scales are parallel.

According to the classical work of the Frenchmen, Soreau and d'Ocagne, four decades ago, for a straight line in cartesian coordinates (figure 2) cutting any three scales u, v and w at $x_1y_1$, $x_2y_2$ and $x_3y_3$, as shown in figure 2, angle a = angle b.

Therefore,

$$y_2 - y_1/x_2 - x_1 = y_3 - y_2/x_3 - x_2$$

Upon simplification of this equation, it is seen that

$$x_2y_1 + x_3y_2 + x_1y_3 - x_1y_2 - x_2y_3 - x_3y_1 = 0$$

which is an expression of the third order determinant

$$\begin{vmatrix} x_1 & y_1 & 1 \\ x_2 & y_2 & 1 \\ x_3 & y_3 & 1 \end{vmatrix} = 0$$

The value of the determinant is the product of all possible combinations of this checkerboard arrangement, with proper regard to sign.

The general constructional determinant, or spe-

cial determinant from which the alignment chart can be more easily prepared, for the third class equation

$$f(u) + f(v) + f(w) = 0$$

is

$$\begin{vmatrix} -\delta_1 & \mu_1 f(u) & 1 \\ 0 & -\left\{\frac{\mu_1\mu_3}{\mu_1+\mu_3}\right\} f(v) & 1 \\ \delta_3 & \mu_3 f(w) & 1 \end{vmatrix} = 0$$

where $\mu_1$ and $\mu_3$ are scale factors and $\delta_1$ and $\delta_3$ distances along the abscissa, selected such that the chart size ensures readability and that

$$\delta_3 = \delta_1 \quad \mu_3/\mu_1$$

In order to apply the principles of Soreau and d'Ocagne to the fourth class equation in spectroscopy, it is necessary to divide it into two third class equations

a log $T\lambda_1$ + b log $T\lambda_2$ = R = $c_1$ — d log $T\lambda_3$

where R is common to both equations. Then, the two constructional determinants for these two equations would be

$$\begin{vmatrix} -\delta_1 & \mu_1 (a \log T\lambda_1) & 1 \\ 0 & -\frac{\mu_1\mu_3}{\mu_1+\mu_3} (-R) & 1 \\ \delta_2 & \mu_3 (b \log T\lambda_2) & 1 \end{vmatrix} = 0$$

and

$$\begin{vmatrix} -\delta_4 & -\mu_4 (-R) & 1 \\ 0 & -\left\{-\frac{\mu_4\mu^5}{\mu_4+\mu^5}\right\} c_1 & 1 \\ \delta^6 & -\mu^6 (-d \log T\lambda_3) & 1 \end{vmatrix} = 0$$

In a like manner, the constructional determinant for the cytochrome C—hemoglobin—myoglobin system could be determined from the equation

$$c_{\text{cytochrome C}} \text{ (moles/liter)} = 9.03 \cdot 10^{-5} \log T^{532.5\text{mu}} - 2.90 \cdot 10^{-5} \log T^{550\text{mu}} - 6.45 \cdot 10^{-5} \log T^{520\text{mu}}$$

and the alignment chart (figure 3).

To read this chart, two isopleth or index lines

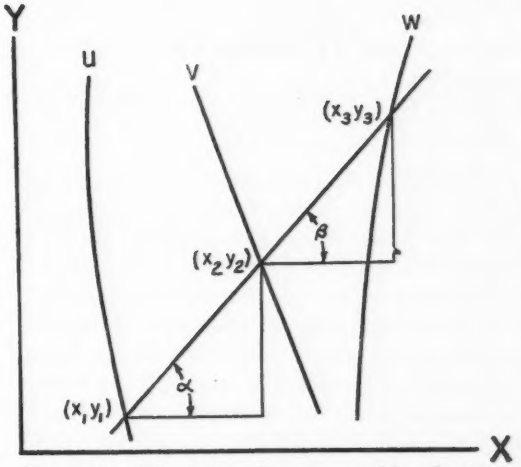


Figure 2. **Principles of nomographic charts in cartesian coordinates.**

$$Ccy\,(\text{moles/l}) = \frac{-4.5 \text{ Log } Tt^{5500} - 10 \text{ Log } Tt^{5200} + 14 \text{ Log } Tt^{5325}}{155.1 \cdot 10^3}$$

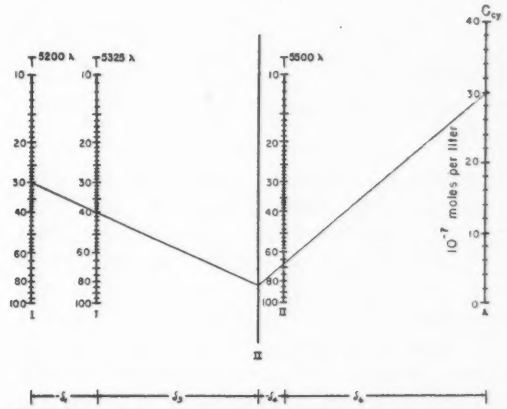


Figure 3. **An alignment chart for a cytochrome C—hemoglobin—myoglobin system.**

are used, one joining the I scales and the other the II scales. The answer is read on A scale.

It is easily seen, then, why nomogram and isopleth are derived from the Greek words nomographia and isoplethes which mean draw a law and equality, respectively. A law is drawn by a line cutting the axis at equal equality.

The application of this type of absorption spectroscopy to clinical analytical problems is yet an unexplored field.

# Abstracts

POLIOMYELITIS. Studies on the Inciting Agent and Specific Serum Treatment. E. C. Rosenow, Lancet. Vol. 246, April 1944.

DR. ROSENOW of the experimental division of the Mayo foundation has recently presented some very interesting and illuminating work on the etiologic agent of poliomyelitis. By the use of dextrose-brain broth, a highly specific type of very small anaerobic Streptococcus organisms was found to be isolated consistently from tissues, fluids, and other materials in which the commonly considered virus was demonstrated. From the study of 37 widely separated epidemics and Rhesus monkey experimentation, these microdiplococci have been repeatedly seen to be filterable along with the active virus.

It is very significant that ordinary aerobic culture for streptococcus organisms is inadequate for growth of these organisms. This organism was found to have a specific affinity for the anterior horns of the spinal cord producing typical flaccid paralysis in experimental animals. Furthermore, the viability of virus and anaerobic streptococci ran closely parallel for as long as 5 years in tissue culture.

Monkeys which recovered from paralysis after inoculation with these streptococci and those thoroughly vaccinated with vaccine derived from them, often became immuned to the virus far in excess of controls. Highly specific serum was developed by inoculating horses for long periods with these organisms as the antigens. The use of this serum in 20 human epidemics strongly suggests the causal relationship of this organism to the disease from the favorable results obtained. These results were also found to show the far better results obtained from earlier administration in the course of the condition.

By special cultural methods, increasing sizes of these organisms ranging from that of the virus to that of the streptococcus were seen, suggesting that the streptococcus here involved may actually be derived from a polymeric growth of the virus. This organism is constantly isolated from the nasopharynx of poliomyelitis patients while ill with the disease, and not before or after the illness. Also it is found in a much greater percentage of well persons during the summer months when poliomyelitis epidemics are prevalent than in other parts of the year. This organism has also been found absent in places remote from epidemics.

The results of these studies indicate that the inciting agent of poliomyelitis represents interrelated stages of streptococci and what is now considered a virus due to its filterability. The streptococcus also appears to play a primary role in the causation of the disease while the virus is a highly invasive, non-antigenic phase of the streptococcus. This work suggests a rather revolutionary concept of our present understanding of microorganisms and definitely needs confirmation.

* * * *

NEW POWDER FOR FUNGUS INFECTION. Report of Research Division, Bureau of Med. and Surgery, Hospital Corps Quarterly, January 1946.

A new preparation for treatment of fungus infections known as undecylenic powder was tested in a study involving more than 5600 Navy men, in Florida.

In a preliminary report it was shown that on a comparative fungistatic basis in prophylaxis and treatment, undecylenic acid and propionic acid and their salts are superior to the commonly used boric-salicylic acid powder.

In the prophylactic study, undecylenic powder showed a significant superiority to both boric-salicylic acid and sodium propionate powder; the latter two showing about equal efficacy. The decreased incidence of infection over that of a control group by the use of undecylenic powder was 85.8% in foot infections and 93.3% in groin involvement.

The results obtained in the active therapeutic use against foot and groin infections followed the same trend as shown in the prophylactic studies. In this study the ointment rather than the powder form was used. Due to the hygroscopic property of sodium propionate powder, the calcium and zinc salts were used and proved more effective, but still distinctly inferior to the undecylenic preparation. Another undesirable property of the propionate powder or ointment is its mild irritative property upon application.

There was an apparent superiority in the use of undecylenic ointment over that of powder in the treatment of foot infections, but this may be due to the fact that those using the former had sought relief from definite symptoms and thus applied greater diligence in their therapeutic measures.

The use of this new agent as a dusting powder for prophylaxis and as an ointment for active therapy of existing fungus infections, holds promise as being our most potent weapon yet known for combating the extremely common cutaneous mycotic infections.

S. I.

* * * * *

FOLIC ACID THERAPY IN THE ANEMIAS OF INFANCY AND CHILDHOOD. Wolf W. Zuelzer, M.D., J.A.M.A., 131:1, 7-8, May 4, 1946.

Folic acid has been shown to be a specific for certain types of anemias with megaloblastic blood formation both in infants and adults.

The anemic syndrome for which folic acid is effective in infants is briefly characterized hematologically as follows: severe normochromic usually macrocytic anemia, leukopenic and neutropenic tendency with giant metamyelocytes and hypersegmented neutrophils in the peripheral blood, thrombocytopenia often with increased bleeding tendency, and atypical bone marrow pattern resembling that seen in relapse of Addisonian pernicious anemia. The clinical picture encountered is of a varied nature resembling other types of anemias inconstantly.

Twenty-nine patients with the designated megaloblastic anemia of infancy were studied. Twelve were given folic acid or the "L. casei factor." Nine gave an unequivocally fine reticulocyte response followed by a return of normal bone marrow pattern of erythropoiesis; the other four died of severe intercurrent infections.

It was definitely shown that the folic acid has no effect on any type of anemia in infancy and childhood in which there is a normoblastic bone marrow present. This agrees with the results in adults as previously shown by Spies and his associates.

The characteristic abnormal marrow pattern is concluded as the essential basis for diagnosis of megaloblastic anemia of infancy arising on a basis of folic acid deficiency.

S. I.

BILATERAL OPTIC ATROPHY AS A SEQUELA TO THROMBOCYTOPENIC PURPURA by P. Carelli, M.D. and J. P. Cangelosi, M.D.; Journal of the American Medical Association, Oct. 20, 1945. Vol. 129, pp. 550-551.

Cases of intracranial hemorrhage following thrombocytopenic purpura have been occasionally reported in the literature. Papilledema or "choked disk," though infrequent, may also accompany this condition, and is more common than bilateral optic atrophy, which is quite rare as a sequela to thrombocytopenic purpura.

Drs. Carelli and Cangelosi report a case of a white boy, age 6, who developed acute, uncontrollable epistaxis following an acute respiratory infection. The platelet count was reduced, and the condition diagnosed as thrombocytopenic purpura. Snake venom, adminstered hypodermically, along with vitamins C and K did not prove fully effective, since within two weeks after the onset, the child developed eyeground changes as well as signs of bilateral optic atrophy, assumed to be on a hemorrahagic basis. Following spenectomy, however, the blood picture returned to normal, and the child improved completely with the exception of the eye findings which remained unchanged.

S R.

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There can be no new qualities in our civilization till there are new qualities in our minds and hearts.—James Hilton.

* * * * *

Thomas L. Brunton discovered in 1867 that amyl nitrate was effective in relieving angina pectoris attacks.

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*"All Army fliers," says Col. Walter S. Jensen, Deputy Air Surgeon, U. S. Army Air Forces, "must have three sights—visual sight, foresight and insight. The forces of gravity preclude hindsight."*

* * * * *

No capable surgeon while cuttin'
A goitre, would slice out the button
We call parathyroid,
So near to the thyroid.
And carelessly say it was nuttin'.

*The relationship of rheumatic fever and tonsilitis was first called to attention by the French physician, Armand Trousseau, in* 1861.

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## ALUMNI—

(*Continued from page* 17)

on Wednesday, April 10th. We wish your family of three all the luck in the world.

1944—Dr. Arthur J. Zweibel is now associated with Dr. Rudolf Dreikurs, Professor of Psychiatry at The Chicago Medical School, with office at 25 E. Washington Street. Dr. Zweibel is also an instructor in Psychiatry at The Chicago Medical School.

The *Quarterly* is very pleased to learn that Dr. and Mrs. Bertram Moss are expecting an addition to their family in February.

Dr. Irwin S. Rabeau has received a commission in the U. S. Public Health Service. Dr. Rabeau is stationed at Juneau, Alaska.

We were happy to hear the Dr. Daniel Roth has opened an office at 403 Collinsville Avenue, East St. Louis, Illinois, for the practice of medicine and surgery. Best wishes for a thriving practice, Dr. Roth.

Also opening a new office is Dr. E. J. Felderman at 1200 N. Ashland Avenue, Chicago for the practice of general medicine. Good luck to you, Dr. Felderman.

* * * * *

Shakespeare on inebriation and coitus—

Macbeth (Act 2, Scene 3):

Macduff: *"What three things does drink provoke?"*

Porter: *"Merry, sir, nose painting, sleep, and urine. Lechery, sir, it provokes and unprovokes; it provokes the desire, but it takes away the performance."*

*A wheel revolving at the rate of* 57,000 *revolutions a minute, making a razor blade travel at the speed of* 1,100 *feet a second is used in high-speed microtomes in making ultra thin sections of plant and animal tissue for examination with the electron microscope. Slices cut by the fast-moving blade range from one micron down to a tenth of a micron in thickness or* 1/500 *of the diameter of a moderately coarse hair.*

*Oxygen therapy was introduced by Beddoe whose publication in* 1794, *in collaboration with James Watt (inventor of steam engine), entitled "Considerations on the Medicinal Use and Production of Factitious Airs" might be considered the beginning of inhalation therapy.—Goodman and Gillman.*


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*We are really very modest—*

but it is no use denying that we are very pleased with, and slightly proud of, the way you have received the QUARTERLY. Your letters have been unanimously complimentary, your comments heart-warming. We thank you.

Especially do we derive deep satisfaction from supplying to you who are in the armed forces the measure of diversion and enjoyment that you have told us the QUARTERLY brings you. We intend to get the QUARTERLY to you, wherever you are, if it is at all possible, and whether or not you are active subscribers. Thus, we may feel that we are helping you, in a very slight way, to do the grand job that you are doing, at and behind the fronts.

But the QUARTERLY cannot be published with good wishes alone. We ask those others of you, who are fulfilling the equally important task of maintaining civilian health, to support this publication so that it may continue to bring you and our graduates in the service into closer touch with The School and each other.

Sincerely,

The Editor

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.....

*Time was when portly Doctor Lance*
*Could spot anemia at a glance;*
*But his most fertile source of tips*
*Is blocked since woman paints her lips.*
*So he a fingertip must probe in*
*To estimate her hemoglobin,*
*And finds oft times the ruddy paint*
*Makes women look like what she aint.*
*—Bull. Acad. Med. Cleveland*

* * * * *

Molinetti thought that the glands functioned during fetal life to draw blood from the kidney and prevent the formation of urine by the fetus, whereas Von Helmont believed the adrenals secreted a substance which prevented the formation of renal calculi.

The ancient Lydians and Medes cemented friendships by drinking blood—Herodotus.

Galenical preparations of belladonna have been employed in medicine for many centuries and were known to the ancient Hindus.

"Eighty-five percent of diseases anyone can diagnose and 15 percent no one." — Dr. David Edsall.

Squill was known as a medicine to the ancient Egyptians and is mentioned in the Ebers Papyrus (1500 B.C.).

It is almost as important to know what kind of patient has the disease as what kind of disease the patient has.

Man is the only animal with a jutting chin.

. . . . .

Nowadays, it seems there are only two classes of patients: those who are benefitted by the sulfonamides, and those who need a doctor who can make a diagnosis.—North Carolina M. J.

Nothing can come of nothing any more than a thing can go back to nothing.—Marcus Aurelius.

Death is fortunate to the infant, bitter to the young man, too late for the old.—Publius Syrus.

It takes sixty-five muscles of the face to produce a frown, and only fourteen muscles to produce a smile.

For the physician there is only one rule: put yourself in the patient's place.—Lord Lister.

Age lends the graces that are sure to please;
Folks want their doctors mouldy, like their cheese.

—O. W. Holmes


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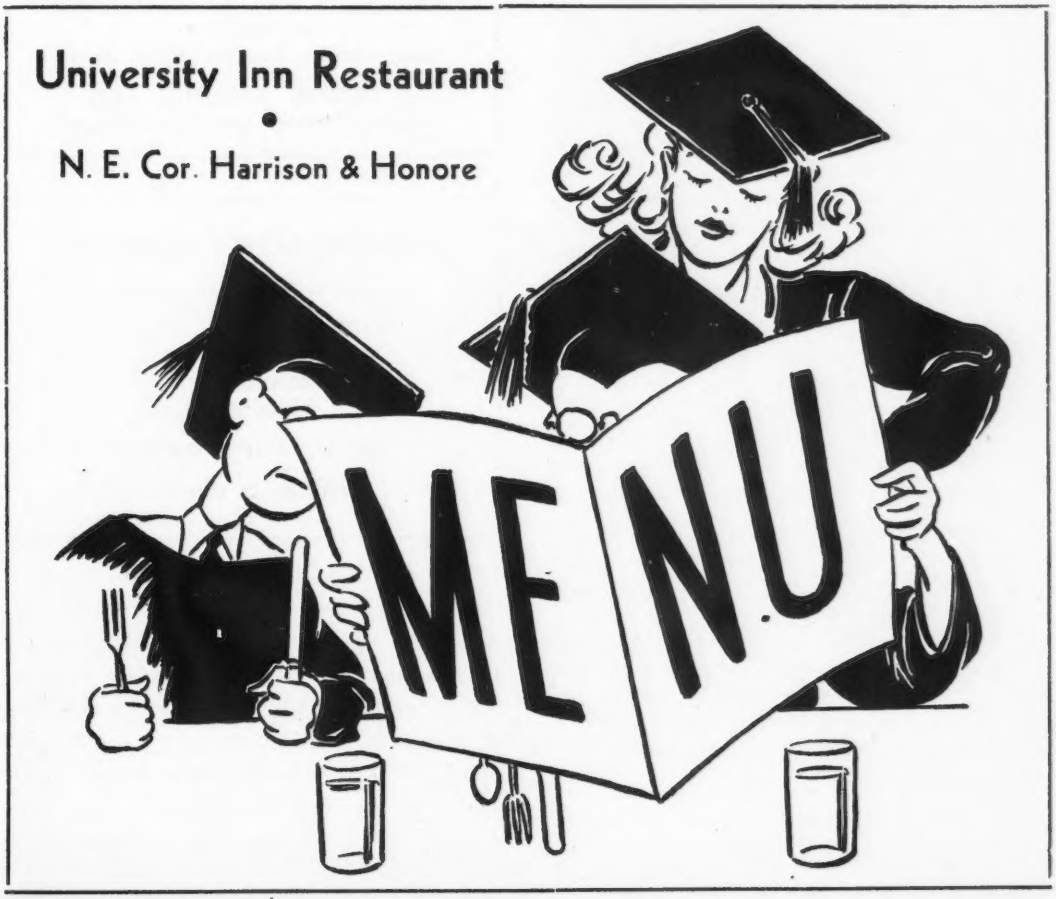
*The greatest and most dangerous disease, and the one that proved fatal to the greatest number, was the consumption. With many persons it commenced during the winter, and of these some were confined to bed, and others bore up on foot; the most of those died early in spring who were confined to bed; of the others, the cough left not a single person, but it became milder through the summer; during the autumn, all these were confined to bed, and many of them died, but in the greater number of cases the disease was long protracted. Most of these were suddenly attacked with these diseases, having frequent rigors, often continued and acute fevers; unseasonable, copious, and cold sweats throughout; great coldness, from which they had great difficulty in being restored to heat; the bowels variously constipated, and again immediately in a loose state, and towards the termination in all cases with violent looseness of the bowels; a determination downwards of all matters collected about the lungs; urine excessive, and not good; troublesome melting. The coughs throughout were frequent, and sputa copious, digested, and liquid, but not brought up with much pain; and even when they had some slight pain, in all cases the purging of the matters about the lungs went on mildly. The fauces were not very irritable, nor were they troubled with any saltish humors; but there were viscid, white, liquid, frothy and copious defluxions from the head. But by far the greatest mischief attending these and the other complaints, was the aversion to food, as has been described. For neither had they any relish for drink along with their food, but continued without thirst. There was heaviness of the body, disposition to coma, in most cases swelling, which ended in dropsy. They had rigors, and were delirious towards death.*—From Hippocrates, *Third Book of the Epidemics.*

* * * * *

"A pretty good doctor is like a pretty good egg. No one wants a pretty good egg for breakfast."

Although para amino benzene sulfonamide (Sulfanilamide) was first prepared in 1908 by Gelmo in the course of his investigations on Azo dyes, a quarter of a century was to pass before its utilization for the chemotherapy of human bacterial infections.

If politicians looked after mental patients they would prepare speeches exhorting manics to calm down and would deliver them during the depressed stage; and then, overcome by the awful hopelessness of their condition, they would make plans to cheer them up, which, of course, would operate in the manic stage.

—Lancet

*The superior doctor serves the nation; the middle grade doctor, the individual; the inferior doctor treats actual sickness.*

*—Chinese Proverb*

Even when the physician sees that death is approaching, he still says to the patient, "Eat this and abstain from that, drink this and not that," but he does not say "your end is near," and it rebukes the prophet in Isaiah in the name of King Hezekiah for telling him bluntly, "set thy house in order for thou shalt die and not live."

Midrash of the Talmud

*"Use purgative medicines sparingly in acute diseases, and at the commencement, and not without proper circumspection."*

*—Hippocrates*

"The truth in medicine is a goal that one cannot attain, and everything that is written in books is worth much less than the experiences of a physician who reflects and reasons."

—Libes ad Abmansorem

Poem from 15th Century Spanish Manuscript:

The fool despises the physician
And does not look to him for help
He ascribes to nature
All cures and healing
He denies the evidence
The Lord placed in this law:
"For the Doctor shall pay."

*"In acute diseases it is not quite safe to prognosticate either death or recovery."*

*—Hippocrates*

*A Poet's Psychology*

A man's nature is best perceived in privateness, for there is no affectation; in passion, for that putteth a man out of his precepts, and in a new case or experiment, for there custom leaveth him.—Francis Bacon.

*"Pains and fevers occur rather at the formation of pus than when it is already formed."*

*—Hippocrates*

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What does it all mean? What does the word "life" mean to us? A feast? No. Work? No. A battle? Oh, no! Life is something merely tiresome, dull, a kind of heavy burden. In carrying it, we sigh with weariness and complain of its weight. Do we really love life? The love of life! The very word sounds strange in our ears! We love only our dreams in the future, and this love is Platonic, with no hope of fruition.